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Volume 103 Part I March 1980

Joint Position Sense: the Effects of Muscle Contraction. W. Z. Rymer and A. D'Almeida 1

Brain Control of Conjugate Horizontal and Vertical Eye Movements: a Survey of the Structural and Functional Correlates. Morris B. Bender 23

Supranuclear Palsy of Eyelid Closure. R. W. Ross Russell 71

Vision in the Temporal Crescent in Occipital Infarction. Sarah Benton, Ivor Levy and Michael Swash 83

Word-form Dyslexia. Elizabeth K. Warrington and Tim Shallice 99

Disordered Inhibition in Internuclear Ophthalmoplegia: Analysis of Eye Movement Recordings with Computer Simulations. Steven E. Feldon, William F. Hoyt and Lawrence Stark 113

Variability of Visual Threshold in Multiple Sclerosis: Effect of Background Luminance on Frequency of Seeing. V. H. Patterson, D. H. Foster and J. R. Heron 139

Chronic Migrainous Neuralgia: a Variant of Cluster Headache. J. M. S. Pearce 149

Neuropsychological Functions in the Follow-up of Transient Global Amnesia. A. Mazzucchi, G. Moretti, P. Caffara and M. Parma 161

Neurochemical Alterations in Huntington's Chorea: a Study of Post-mortem Brain Tissue. E. G. S. Spokes 179

Notices of Recent Publications 211

Forthcoming Events 219

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Notices of Recent Publications 211

Forthcoming Events 219

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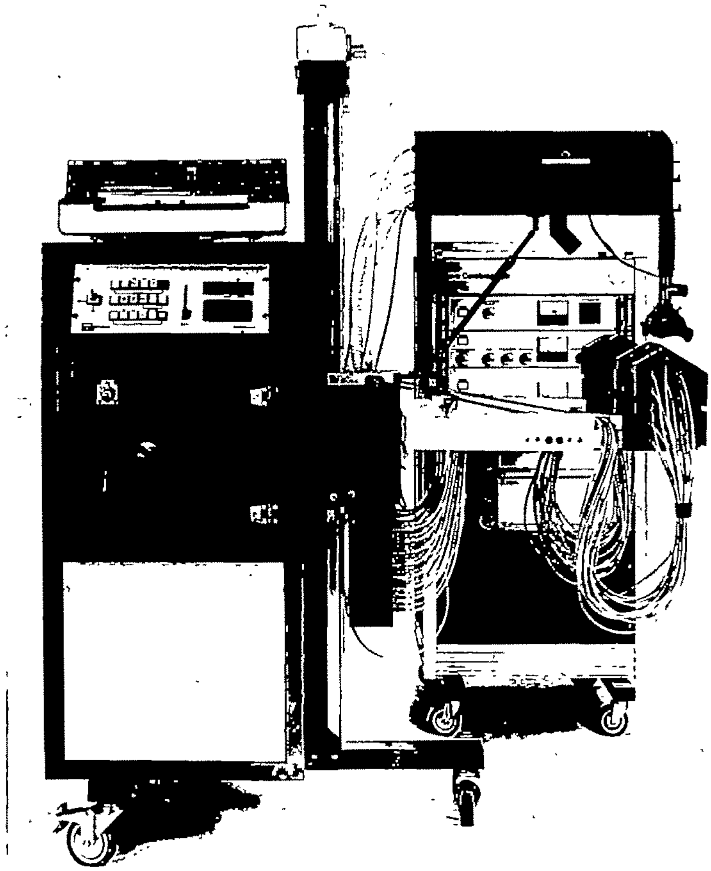

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JOINT POSITION SENSE
THE EFFECTS OF MUSCLE CONTRACTION

by W. Z. RYMER[1] *and* A. D'ALMEIDA

(*From the Department of Neurosurgery, Neurosurgery Laboratory, Upstate Medical Center,*
Syracuse, New York 13210, USA)

INTRODUCTION

THE receptor origins of static positional sensation remain uncertain. Until quite recently, joint sensation was attributed exclusively to the various articular receptors, which were considered to be differentially sensitive to joint position and its angular derivatives (Andrew and Dodt, 1953; Boyd and Roberts, 1953; Skoglund, 1956, 1973; Godwin-Austen, 1969). Joint afferent information was thought to project centrally *via* the dorsal columns and medial lemniscus to the ventrobasal complex of the thalamus (Mountcastle, Poggio and Werner, 1963), and somatosensory cortex (Mountcastle and Powell, 1959; Mountcastle *et al.*, 1963). This general scheme has been seriously challenged by recent work, which has demonstrated the apparent inadequacy of articular receptor discharge as the source of joint positional information (Burgess and Clark, 1969; McCall, Farias, Williams and BeMent, 1974; Clark and Burgess, 1975; Grigg, 1975) and a corresponding lack of static sensitivity in joint-related neurons of the dorsal column nuclei (Williams, BeMent and Yin, 1974) and thalamus (Yin and Williams, 1976). It appears that articular receptors responding to maintained joint position in the mid-range are few in number; most respond only to the extremes of movement and usually show bidirectional sensitivity. Accordingly, on current evidence, there appears to be no group of joint receptors capable of uniquely specifying static joint angle over the physiological range of motion.

This lack of suitable joint receptors is not reflected in any decline in positional sensitivity in the mid-range of human joint motion. Human subjects can recognize small maintained joint deviations in this region, even after prolonged periods of time (Horch, Clark and Burgess, 1975); in fact, static deflections are appreciated even when the causally related movements are not (Horch *et al.*, 1975).

In recent years, muscle spindle receptors have been advanced as a candidate source of limb positional information, partly because articular receptors seemed inadequate, but mostly because new evidence supporting their contributory role has been forthcoming (*for review see* Matthews, 1977; McCloskey, 1978). This evidence is quite diverse in nature, arising from studies on vibrated muscle (Hagbarth and Eklund, 1966; Goodwin, McCloskey and Matthews, 1972*a*; Craske, 1977), anæsthetized digits (Goodwin *et al.*, 1972*a*, *b*)., prosthetic joints (Cross and McCloskey, 1973; Grigg, Finerman and Riley, 1973), as well as from studies using normally contracting muscle in intact subjects (Browne, Lee and Ring, 1954; Craske and Crawshaw, 1975; Gandevia and McCloskey, 1976) and operatively exposed muscle tendons (Matthews and Simmonds, 1974).

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[1] Present address: Department of Physiology and Neurology, Northwestern University Medical school, Ward 5-319, 303 E. Chicago Ave, Chicago, Illinois 60611.

Although the accumulated evidence seems to support some type of muscle afferent contribution to the perception of limb position, several major problems require clarification. Most particularly, the signal arising out of muscle spindle receptors is not uniquely determined by joint angle (or muscle length), because receptor discharge may reflect both externally and internally imposed changes in intrafusal fibre state. In human finger flexors, for example, it has been shown that spindle receptor discharge rate rises rapidly when the muscles are contracted isometrically (Vallbo, 1971, 1974). This dilemma is of course not unique to spindle receptors—similar uncertainties arise with regard to any sensory receptor which receives efferent innervation, or which is activated as a consequence of willed movement. The lack of sensory error in these circumstances is often ascribed to 'efference copy' or 'corollary' innervation.

Nevertheless, if muscle receptor afferents contribute to joint position sense, then the competing effects of externally *versus* internally (fusimotor) imposed changes provide a potential source of conflicting information, and therefore of errors in perceived limb position. The marked increase in spindle receptor discharge recorded during isometric voluntary contraction suggests that substantial errors of perceived limb position could occur under such conditions. Alternatively, the consequences of increased fusimotor activation could be nullified by central processing, perhaps *via* an efference copy mechanism, or *via* some force-related afferent input.

We have investigated the effects of varying muscle force on perceived joint position as a means to examine the muscle afferent contribution to joint positional sensation. The proximal interphalangeal joint of the right index was flexed or extended by an electromagnetic device, and perceived position was estimated from matched movements of the equivalent joint on the left index. We found that when the loaded finger was able to move, finger position was accurately perceived; however, when the subject was required to generate isometric flexion force across the deflected joint, gross errors of perceived position occurred. These errors were in the direction of increased flexion (flexor muscle shortening) rather than toward muscle elongation, as would perhaps have been expected from the results of previous vibration and loading experiments (Goodwin *et al.*, 1972*a*; Eklund, 1972; McCloskey, 1973). Similar effects were noted during anæsthesia of the digit.

The hypothesis is advanced that the sensation of joint position may be a 'derived' quantity, computed from length and force-related muscle afferent signals.

METHODS

Experiments were performed on 12 normal human subjects (10 male, 2 female) ranging in age from 24 to 38 years; each subject was not examined with the full experimental protocol. Subjects were recruited from laboratory personnel and graduate students.

Arrangement of the Experimental Apparatus

In a typical experiment, the subject was seated with both forearms resting symmetrically on a low table. Each forearm was supported by a ventral cast which extended from just below the elbow joint across the wrist and metacarpophalangeal joints. Immobilization was ensured by bandaging each forearm and hand to the cast. The proximal phalanx of each index was further stabilized with the aid of a small padded clamp, which included the cast projection and the proximal phalanx within its circumference. The distal portion of each index was enclosed in a light padded cylindrical metal frame, which extended from a point approximately 1 cm distal to the proximal interphalangeal joint to the tip of the finger. This frame prevented motion of the distal interphalangeal joint, and served as a point of attachment for mechanical actuators or transduction devices. At the mid-point of each frame was attached a small universal joint and rod through which other devices were quickly connected.

In all experiments, the right index was attached *via* the joint and rod to an electromagnetic motor (Electrodyne AV-50) capable of a linear motion of 10 mm which, given the point of attachment to the finger, proved equivalent to a maximum angular deflection of 25 degrees. A pair of strain gauges was inserted at the point of attachment of the connecting bar to the motor shaft; these gauges provided force recordings and a feedback signal allowing the motor to be configured in force-feedback mode as required.

A length transducer, placed in parallel with the motor shaft, provided a position signal, which was used for experimental records and for feedback purposes. In most of our experiments, finger position was maintained in the face of varying force by servo-regulation of motor shaft position.

Although motor shaft motion was linear, we chose to convert the linear measure to angular notation for ease of comparison of right and left finger motion—this transformation was achieved by a linear scaling operation only. The use of a simple scale proved acceptable because the range of angular motion was a relatively small (20 degrees) and because the motor was placed so as to maximize the linearity of the relationship.

In many experiments the left finger was attached (*via* the mental frame) to a smaller pen motor (derived from a Grass pen recorder) which provided controlled angular motion, again over a range of 0 to 25 degrees. This pen motor had limited torque output and as a consequence, was used strictly to impose passive movements on the left index. Left index movement records were provided by a separate length transducer. Recordings of right index and left index movement, together with right finger force were displayed on monitor oscilloscopes and were also output on to a strip chart recorder (Grass 8 channel); these chart recordings were used for later detailed measurement and analysis.

Finger movements were imposed by using ramp and hold signals derived from a signal generator, with variable rate and amplitude setting. In some experiments in which movements were imposed upon both right and left index fingers, two similar function generators were used. The velocity of movement remained constant for each experiment and was chosen so as to substantially exceed the perceptual threshold; in most experiments velocity of motion lay between 5 deg/s^{-1} and 10 deg/s^{-1}. The periodicity of the movements was usually established by a master timing device (digitimer—Devices Ltd.)—a typical cycle time was 20 s. Ramp onset, hold, and offset duration were also under digitimer control as was the total number of cycles in each sequence—typically 22. In some experiments movement velocity remained constant but the movement amplitude was changed with the help of a manually adjustable 'clip' function which simply decreased the ramp duration. A number of different types of experiment were performed; however, many displayed common features. As an illustration, one typical experiment incorporating many of these features will be described in some detail.

Perception of Position of the Right Proximal Interphalangeal Joint with Varying Force Loads on the Right Finger

In this experiment, movements are imposed upon the right index by varying the load force. The large electromagnetic motor is here configured in a force-feedback mode, allowing the subject to move the right finger at will simply by exerting sufficient force. The left index is attached to the length transducer only.

At the beginning of each trial the subject is required to place the right finger at a specified joint angle. The subject cannot see either finger; both actual and required position of the right index finger are given by a visual display on an oscilloscope monitor which the subject faces. When the required angle has been achieved for several seconds, the ramp generator is triggered, and there follows a rapid ramp increase or decrease in force which causes the finger to assume a new position (towards either flexion or extension). The display monitor is blanked during the perturbation, to eliminate visual cues. The subject is instructed specifically not to intervene voluntarily at any stage. As a result, the finger quickly attains a relatively stable equilibrium, at which point the subject is required to match perceived finger final position with appropriate movements of the left index. After 22 trials, the subject is allowed to rest for five minutes before commencing the next sequence. A maximum of six sequences was used at any one sitting and subjects were not examined for more than one hour on any occasion. The duration of testing was curtailed if signs of fatigue, manifested as subjective discomfort or as an inability to support the higher static loads, became evident.

Local Anæsthesia

In order to investigate the perception of finger movement and position in the absence of joint and cutaneous sensation, right index sensation was eliminated in three subjects. Local anæsthesia was induced by injecting 5 to 15 ml of 1 per cent aqueous xylocaine around the base of the finger, concentrating particularly on the region near the digital nerves. Total loss of sensation to all modalities was achieved within ten to fifteen minutes but was relatively short-lived (thirty to fifty minutes), limiting the number of different experiments which could be performed within the time available.

Data Analysis

The major variables, right and left finger movement amplitude and right finger force, were measured directly from the strip chart recordings. The relationship between these variables was plotted and evaluated with a range of techniques including covariance and least squares regression. Comparison between different slopes and intercepts was based on both slope and intercept confidence limits (estimated using t tests) and analysis of variance of the regression.

RESULTS

In most of the experiments to be described, the perceived position of the proximal interphalangeal joint of one index finger was estimated by measuring the subjects' voluntary movement of the equivalent joint on the other index, with the subject instructed to match maintained finger position (*see* Methods). The perturbed or 'test' joint was usually on the right hand, and the 'tracking' joint on the left. Our experiments compared the joint position perceived when the test finger was loaded, but free to move, with the sensations recorded when the same joint was physically constrained—under the latter condition, the long finger flexors are active, but in an approximately isometric state. Such a comparison was rendered possible by the design of our perturbing device, which could be configured in length-feedback (preventing motion) or force-feedback (allowing motion) modes (*see* Methods). The effects of additional interventions such as local anæsthesia or vibration of the test digit were also examined using this general paradigm.

Perception of Passive Joint Motion

In order to evaluate the effects of changing load force on perceived joint position, it was first required that our subjects' perceptual capacities for simple, passive joint motion be defined in our experimental setting. In most cases, these determinations preceded other force-related experiments. In nine subjects, we imposed flexion and extension movements of differing amplitude on the proximal interphalangeal joint of the right index finger. These movements were applied at a constant velocity (typically 5 deg/s^{-1}) terminating after a variable interval: each new position was then held for approximately 5 s. The subjects were instructed to ignore the actual motion, and to reproduce the maintained position of the test finger, beginning about 1 s after ramp termination.

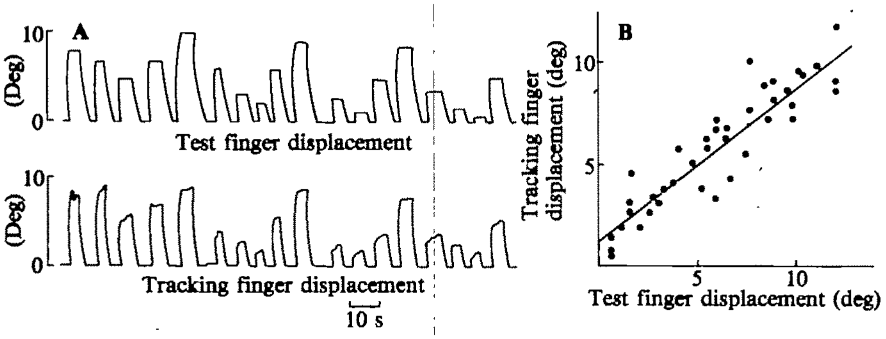

FIG. 1. Perception of passive movements of the right index estimated from matched movements of the left index finger. A depicts a sequence of trials, in which the motion of the proximal interphalangeal joint of the right index (test finger), is illustrated above, and perceived motion, as reflected in movements of the proximal interphalangeal joint of the left index (the tracking finger) is shown below. In B, tracking finger (left index) movement is plotted on the ordinate, and test finger (right index) movement on the abscissa, for a sequence of forty trials collected from the same subject at one sitting. The line, fitted by least squares, has slope 0.76, and ordinate intercept 1.13 (F test for significance of the regression $P < 0.01$).

In all nine subjects, passive movements of the proximal interphalangeal joint of the right index, applied over a range of 1 to 20 degrees, were accompanied by proportionate movements of the corresponding left index joint. Fig. 1A shows a typical series of flexion responses from one subject, in which the test finger perturbations are shown in the upper trace and the corresponding tracking movements below. In fig. 1B, the amplitude of the tracking response is plotted against the test movement for all experimental trials collected in the same subject at one sitting; the relation is well described by a linear equation with slope of 0.76 and ordinate intercept 1.13 degrees.

The relations were acceptably linear in all nine subjects examined, but in eight of these, the slope factor was less than 1 (range 0.58 to 0.91); the ninth had a slope of 1.0. The mean slope value was 0.69 (n = 9), and the mean ordinate intercept 2.0 degrees (range −1.5 to 5 degrees). We did not attempt to measure the threshold of movement detection specifically, since we were more concerned with magnitude estimation; however, it was found that all nine subjects were unable to recognize reliably the presence or absence of movement of less than 1 degree. These threshold values are commensurate with those reported elsewhere (for example, Kokmen, Bossemeyer and Williams, 1977).

Perception of Motion Imposed Upon a Finger Generating Maintained Force

In an attempt to assess the effect of operating force upon the perception of joint position, the test finger movements were imposed with the finger counterbalancing a background force, which varied from 0 to 5 N in the course of the experiment. The motor was configured in force-feedback mode.

This experiment requires that the subject first establish some specified initial position of the force bearing (right index) finger by matching a display of actual finger position against required position on a monitor oscilloscope (*see* Methods). At some variable time, a ramp and hold change in force is applied, causing the finger to move to a new position in either flexion or extension: the subject is instructed not to intervene voluntarily at any stage. Under these instructions, the finger usually achieves a new, stable position, which the subject is then required to reproduce, denoting this joint angle with the left index finger, as described previously. (The position achieved does not require voluntary intervention for at least several seconds; rather it appears to be determined by the actions of a central servo-mechanism. *See* Crago, Houk and Hasan, 1976.)

We found that ramp and hold variations in load force produced maintained deflections in finger position, with amplitude proportional to the magnitude of the load change. These changes were accurately reproduced by tracking finger movements in eight different subjects. Fig. 2 compares the responses obtained during declining force ramps in one subject under three types of operating conditions; passive, active low force (null), and active medium force (1.2 N). The slopes of each relation are virtually identical (0.92, 0.94, 1.02) and the intercepts are very close. Overall, the relation describing the perceived position of the force-bearing finger is indistinguishable from that evoked by passive movement of the relaxed finger.

In eight subjects examined with this paradigm (force range 0.1 to 3.9 N) the slopes of the relation between test and tracking finger motion were usually statistically indistinguishable from those observed with passive movement alone (based upon t test comparisons of slopes and intercepts, at the 5 per cent probability level). These slopes ranged from 0.63 to 0.99 in different subjects, and although there was considerable variation in the intercept values (range −1 to −4 degrees) there was no systematic trend in ordinate intercept for different force levels in any one subject.

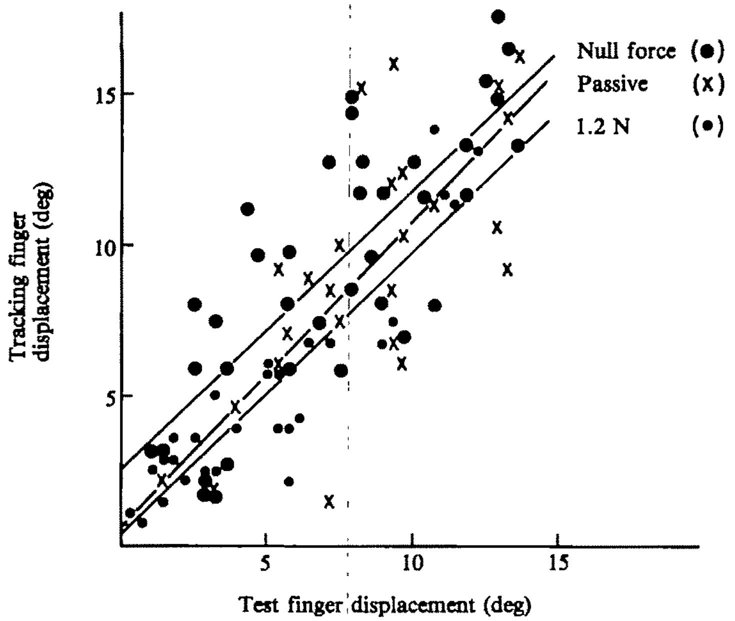

FIG. 2. Perception of joint position in a finger supporting a load. The magnitude of perceived movement (estimated from tracking finger movement) on the ordinate, is plotted against test finger flexion movement (on the abscissa) for three different operating conditions in one subject. These conditions are passive movement (x), very low initial force (termed null, ●), and moderate initial force levels (1.2 N, •). Test finger movements were imposed by introducing ramp and hold decreases in load force, commencing at the same initial force level for a particular sequence of trials. The coefficients of the fitted regression lines are:

Force (*N*)	*Slope*	*Intercept* (*deg*)
Null	0.92	2.6
1.2	0.94	0.4
Passive	1.02	0.6

Regression slopes are not significantly different from each other, but the null intercept is different from that of 1.2 N (t test, $P < 0.01$). However, there was no trend established with increasing initial force, and it is likely that the difference is fortuitous.

Estimate of Joint Position for Voluntary Finger Movements Under Constant Load Conditions

The previous observations, based upon externally imposed finger movements, demonstrate that the perception of joint position is not strongly influenced by operating force. However, we also wished to determine if the force load faced by a finger moving under *voluntary* control could influence the estimate of final position. In this series of experiments, the effect of varying the force against which the *tracking* finger moved was examined. Here, the passive left finger is displaced and held at some specified position for approximately five seconds, during which time the subject attempts to reproduce the perceived position of the left index, with the right finger now working against some predetermined, constant force load.

Two variations on this approach were implemented. The first imposed movements of differing amplitude on the passive left index, while the load force on the right was kept at a constant level for a sequence of trials. The second used constant amplitude movements of the left index, while varying the load force on the right, in successive trials. In these experiments, the left finger movement is being used to introduce a 'reference' signal; the tracking finger is now on the right. The two experiments are clearly closely related and they were found to provide mutually consistent results.

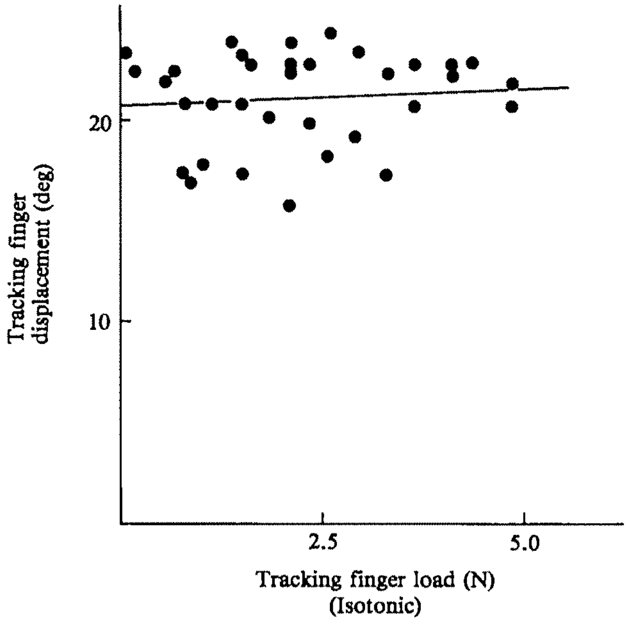

FIG. 3. Lack of effect of varying load on the performance of the tracking (right index) finger. The left index finger is subjected to a repetitive 20 degree movement. The magnitude of perceived deflection is given by right index motion (plotted on the ordinate) with the finger working against different loads in successive trials. Load magnitude is shown on the abscissa. The plot shows that varying the load force supported by the right index does not influence the estimate of left finger position. The relation between perceived motion and test finger force has essentially zero slope (0.06, not significant). The ordinate intercept is 21 degrees.

Constant Displacement Amplitude—Varying Load Force

In fig. 3, different force loads are applied to the right index in successive trials as the subject attempts to reproduce a repetitive constant flexion movement of the left finger (here 20 degrees). It is apparent that these force variations do not alter the perceived position of the right index; the 20 degree movement is consistently reproduced, resulting in a flat relation between perceived position and load force. Essentially similar observations were made in five other subjects, each examined over a wide range of load force (0.1 to 4.5 N). No subject displayed a significant change in perceived joint position with increasing load. For the five subjects examined, the slopes of the relations between perceived movement and force were −0.03, −0.01, −0.9, −0.21, −0.23. No slope was significantly different from zero (t test, 5 per cent level of probability).

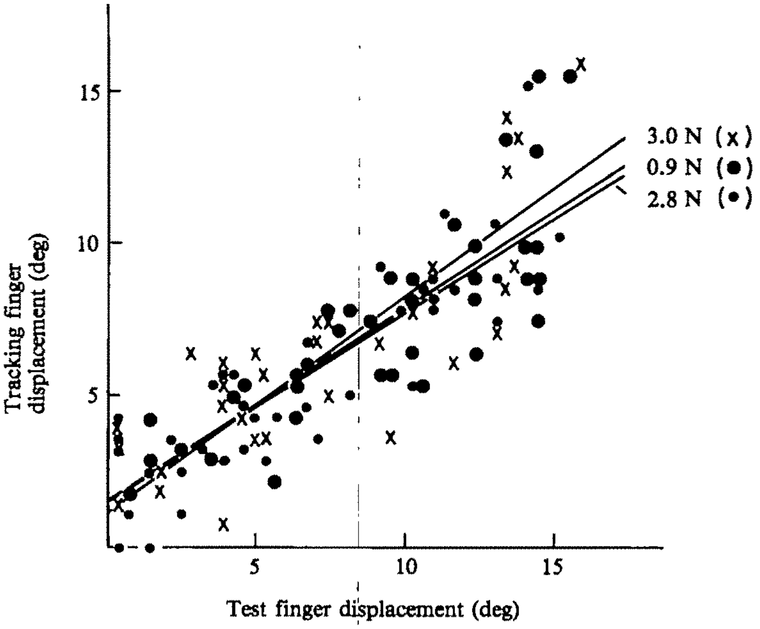

FIG. 4. Lack of effect of load on the performance of the tracking (right index) finger. The left index finger is moved passively over a range of different amplitudes, plotted on the ordinate. The right index moves against a constant load for a sequence of 22 trials. Three different load levels were used; 0.9, 2.8, 3.0 N, as shown in the figure.

Regression coefficients are:

Force (N)	*Slope*	*Intercept (deg)*
0.9	0.64	1.5
2.8	0.61	1.6
3.0	0.65	1.5

Regression slopes and ordinate intercepts are not significantly different from each other (t test, $P < 0.05$).

Varying Displacement Amplitude—Constant Force Load

The results of the second approach, in which varying passive finger movements on the left are reproduced by the right index working against a constant force load are illustrated in fig. 4. Here, both the sensitivity of joint sensation (measured by the slope of the relation between right and left finger motion) and the absolute estimate of joint position (measured by the vertical position of the graph) are again uninfluenced by substantial variations in load force (0.90 to 3.0 N): the various regression lines are statistically indistinguishable (*see legend*). The regression lines calculated in each of the other eight subjects examined were compared at two different force levels (typically 0.1 and 3.0 N) and were also not significantly different from each other in six of eight subjects. Moreover, although in two of eight subjects a comparison of slopes and intercepts at particular high and low force levels showed statistically significant differences, comparable differences were not detectable for slightly different but equally separated forces, and there was no clear trend with changing force. We felt it unlikely that there was a genuine force-related effect.

The preceding results, though derived by using different experimental techniques, have one clear common feature. That is, increasing levels of load force do not greatly influence the perception of joint position when the loaded finger is able to move. When the loaded finger is unable to move, however, entirely different observations ensue.

Effect of Isometric Force Variations on Perceived Joint Position

When the experiment is designed so that the subject is required to produce voluntary isometric force against the device moving the test finger, then major errors in perceived joint position occur. In this paradigm, the puller typically imposes a constant amplitude movement on the right index finger (although the subject does not know that the amplitude is constant). At about the same time that

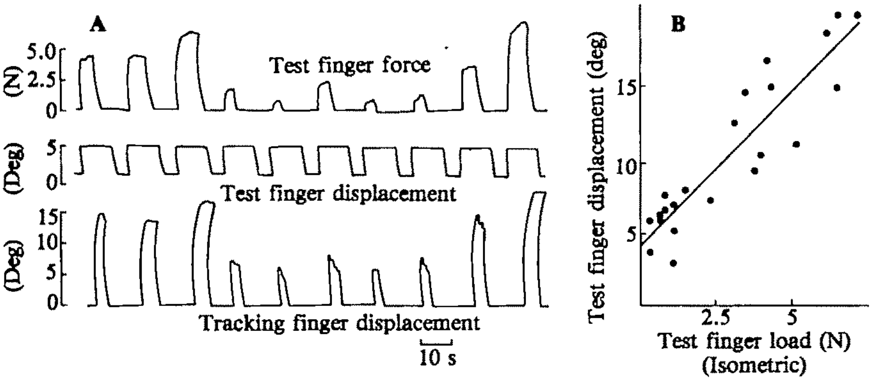

FIG. 5. Production of isometric force interferes with the estimation of joint position. A, The test finger (right index) is subjected to periodic flexion movements of 4 degree amplitude, illustrated in the centre panel. Shortly after onset of movement, the subject increases flexion force on the right index by tracking a visual display of required force on an oscilloscope monitor; the resultant force is shown in the upper panel. The final position of the right index is estimated during the 'hold' or isometric phase of the movement, using matched movements of the left index (tracking finger), depicted in the lower panel. B, Magnitude of perceived motion is plotted on the ordinate and the isometric force on the abscissa for the same subject. The slope of the fitted regression line, which is a measure of error magnitude, is 2.25 degrees/N and the ordinate intercept 4.55 degrees (*versus* 4 degrees actual movement).

the movement is initiated, the subject voluntarily increases the force on the moving finger by tracking a monitor display of required force—this increased force continues during the hold phase of the joint movement (that is, under isometric conditions). Once force and position are stabilized, the subject is then required to reproduce perceived joint position with appropriate movements of the tracking (left) index finger. In many cases, the imposed joint motion commenced just before the increase in force, however, the errors induced were not critically dependent upon the temporal sequence of force and position change. Most frequently, the two events were made to coincide, largely to distract the subjects' attention from the ongoing dynamic phase of movement.

Fig. 5A illustrates a typical series of responses in which, although the stimulus magnitude is held constant at 4 degrees (middle trace), the motion of the tracking finger (lower trace) varies in accordance with test finger isometric force (upper trace). This finding is documented explicitly in fig. 5B which is derived from the same experimental series. Here, increasing isometric force is accompanied by a proportionate increase in amplitude of the perceived motion (even though test movement amplitude remains quite constant in each trial). The relation between perceived position and isometric force is well described by the equation

$$\theta_p = \theta_{\text{intcpt}} + K\Delta F$$

where θ_{intcpt} is the ordinate intercept
θ_p is the perceived position
K is the error slope constant
ΔF is the force increment.

In the illustrated example, $\theta_p = 4.55$ degrees (*versus* 4 degrees actual flexion movement) and $K = 2.25$ deg/N isometric force. Very similar observations were made in five other subjects, each of whom was examined on at least two different occasions. Each subject showed a progressive increase in error towards joint flexion with increasing isometric force, described adequately by a linear relation. The ordinate intercepts and error constants (K), are summarized in Table 1.

Although these results are clear, this experimental paradigm provides several potential sources of error, which must be excluded before the results can be accepted at face value. Most significantly, since the experiment requires the subject to voluntarily increase force with one hand while reproducing estimated joint position with the other, it is possible that the 'descending' instructions interact. The most likely interaction would be that the subject confuses finger position with finger force, and gives an estimate relating to isometric force rather than movement. A second possible interaction is that the perception of movement of the tracking finger might be influenced by the production of force with the other index. These issues were explored in two control experiments.

In the first control, the subject was instructed to establish a specific high level of force with the test finger (typically 5 N) prior to the onset of enforced test-finger movement. As the finger movement commenced, the subject tracked a declining force signal with the test finger toward the final isometric value. When the ramp motion was complete, the force was then isometric. Under these conditions (of declining isometric force) 5/5 different subjects still generated errors closely comparable to those recorded during *increasing* isometric force. The experiments using declining force are marked with asterisks in Table 1—the slopes are clearly comparable with those observed during increasing force.

TABLE 1

Subject	*Hand*	*Test angle (deg)*	θ_{intcpt} *(deg)*	*Error slope (K) (deg/Newton)*
T.D.	R	3.12	7.65	1.35*
		2.88	3.84	1.37*
N.H.	R	4.50	3.12	1.33
		2.88	1.53	1.75*
		4.00	4.55	2.25
M.M.	R	4.32	6.86	0.72
		3.12	2.49	0.69
		3.60	5.26	0.81*
S.W.	R	3.36	4.90	2.36
		3.36	3.20	1.57*
		3.36	5.24	1.51
J.Z.	R	2.16	3.56	1.46*
		2.16	3.04	1.71
		2.16	4.23	1.42
R.S.	R	3.12	0.49	2.18
		3.12	2.18	2.11

Table 1 lists the errors induced by increasing isometric force, as the subject is required to match test (right) index position with appropriate movements of the left (tracking) index. Shown are representative examples of isometric error coefficients (right column), calculated for 6 different subjects. The actual movement amplitude is listed in the third column (test angle). Values for any given subject are given for trials collected on a single day, although all subjects were examined at least twice. The asterisks specify trials with declining isometric force levels (*see text*); the error magnitudes (given by the slope factors) are not significantly influenced by the direction of the force change.

Since the direction of the test movement and the voluntary force change are now opposed, an interaction between the force command and the perception stage should have reduced the error significantly; that this did not happen suggests that the estimates of isometric error were not artifactual. However, since the final outcome required an estimate of finger position to be made during a *constant* isometric force, it is difficult to completely eliminate some cross-modality interaction.

In the second control experiment we examined the possibility that a movement of one index is modified when the subject varies isometric force with the other hand. Four subjects were examined. Each subject was instructed to match isometric right finger force against a display level—no movement of the right index was imposed. The subject was then asked to repeat a movement of constant amplitude with the left finger as right index isometric force was changed voluntarily in successive trials. Under these conditions, no subject showed significant variations in the amplitude of left finger motion.

Another source of error could derive from the compliance of the interface between flexor muscle and puller; this compliance resides in the finger soft tissues and the mechanical finger frame with its attachments. The combined properties of finger tissues and the mechanical attachments were estimated in two subjects by measuring the movement of a skin spot marked over the proximal interphalangeal joint, during successive ostensibly isometric voluntary contractions. Although the initial compliance was significant (because pad tissues were compressible), the net compliance of frame and soft tissues declined sharply at force levels exceeding 0.2 N, providing mean compliance values of the order of 0.1 to 0.3 deg/N over a 5 N force range.

Relative Contributions of Force and Effort to Isometric Error

Although, to this point, the isometric error has been correlated exclusively with changes in force, it is conceivable that the error is better related to the effort expended by the subject. However, this alternative appears unsatisfactory for the following reasons.

First, there appears to be no inherent reason why effort should be greater in isometric rather than isotonic experiments, yet, as we have described, the errors appear quite different under two of the circumstances.

The second reason derives from observations made in fatigued subjects. In three subjects examined with the isometric paradigm, repeated attempts to generate high levels of isometric force were accompanied eventually by increasing fatigue, requiring greater effort for the subject to reach the criterion force levels. Under these conditions, the isometric errors either remained constant, or declined as subject force output decreased, even though associated effort was markedly increased.

Digital Blockade with Local Anæsthetic

Because the muscles responsible for flexion of the proximal interphalangeal joint of the index reside in the forearm, infiltration of the index with local anæsthetic has no effect upon the muscle innervation, a point used to advantage by many prior investigators. It has been shown previously that loss of both cutaneous and deep sensation in the fingers is not accompanied by complete loss of positional sensation (Goodwin *et al.*, 1972*a*, *b*). We wished to verify that observation and to evaluate the effects of isotonic and isometric force variations in the anæsthetized state.

In three subjects, the right index finger was anæsthetized by injecting 5 to 15 ml 1 per cent lidocaine around the base. After a ten to fifteen minute interval, both superficial and deep sensation was entirely lost, yet each subject was able to detect passive finger motion with considerable precision. For example, fig. 6 compares a typical series of responses in which the subject is asked to match passive movements of the right index with appropriate movements of the left index, before (small circles) and after (large circles) the injection with the local anæsthetic; the perception of passive finger movement persists. Furthermore, although there is some increase in the variability of estimated joint position after blockade, the slope values are indistinguishable.

When the subject is asked to reproduce a passive movement of the left finger with the anæsthetized right finger working against a constant load, the slope of the relation between perceived and actual position remains comparable to that observed in the unanæsthetized state, but the ordinate intercept is frequently increased, though in an unsystematic fashion.

Most significantly, if the subject is required to exert isometric force with the displaced, anæsthetized finger, the errors of joint positional sensation recur. In two

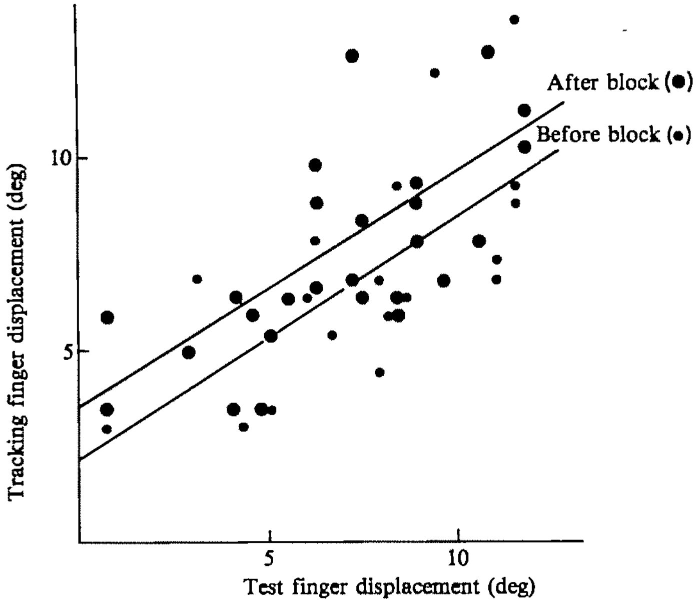

FIG. 6. Anæsthesia of the right index finger does not eliminate the perception of joint position. Passive movement of the right index (test finger), is plotted on the abscissa and perceived motion on the ordinate, before and after the induction of the anæsthetic. The regression lines are almost identical in slope (before 0.62, after 0.60), but differ slightly in intercept (2.1 and 3.4 degrees, in the same order). Slopes are not significantly different (t test, $P < 0.05$).

persons subjected to detailed analysis (the third describing some return of cutaneous sensation during the experiment), the magnitude of the error was 1.46 and 1.96 deg/N, values commensurate with those observed in the unanæsthetized state.

DISCUSSION

The results of this study provide one major finding. If, in the course of an imposed interphalangeal joint movement, a subject exerts substantial isometric flexion force against the perturbing device, the perceived position of the joint is often greatly in error. This error is proportional to the amount of force being exerted and is in the direction of increasing flexion. The latter finding is to be contrasted with the observations made when the joint is allowed to move, even against substantial forces; the error is then insignificant.

Comparison with Previous Observations

Our results are in keeping with those of Monster, Herman and Altland (1973), but are somewhat at variance with those of McCloskey (1973), who found that subjects perceived a loaded limb to be more *extended* than it actually was. In

McCloskey's experiment, the subject was required to estimate limb position with the limb in question supporting a load, an experiment analogous to our study in which the load-bearing right index is subjected to ramp changes in force. The absence of systematic force-related errors in our experiments may reflect a proportionally greater degree of variability in our observations, in that our movements were relatively small (up to 20 degrees), the potential error magnitude modest (typically 2 to 4 degrees for a 50 degree deflection, according to McCloskey), and the sensitivity of perception less acute in more distal joints. In addition, we attempted to establish the perception of joint position over a wide range of movement amplitudes, using regression techniques, rather than comparisons based upon a single joint angle. Since the confidence limits of the regression were often broader than the scatter about a specific intermediate angle, the sensitivity of our methods may have been smaller.

Receptor Sources of Joint Positional Error: Muscle or Joint

Although suggestive of muscle afferent involvement, the force-related changes in perceived joint position cannot automatically be assigned to a muscle afferent source, because other receptors may also have been influenced. For example, joint capsular afferents are known to increase their discharge during contraction of adjacent muscles (Grigg and Greenspan, 1977), although it seems unlikely that muscle contraction will either greatly increase the number of capsular units active in the mid-range of joint motion, or alter their dynamic properties (Grigg and Greenspan, 1977). It should be noted, however, that a detailed examination of joint receptor discharge in the course of normal activity of the surrounding muscles remains to be provided.

It is also conceivable that cutaneous mechanoreceptors may have contributed to the isometric error, though the persistence of such errors in experiments on the anæsthetized finger argues strongly against a central cutaneous role.

None of the cited objections applies to muscle afferents, since both spindle receptors and tendon organs have been shown to increase their discharge during isometric contraction in man (Vallbo, 1971, 1974; Burke, Hagbarth, Lofstedt and Wallin, 1976). Based on the dual counts of sensitivity to joint movement and operating force it appears that a muscle afferent contribution is the most plausible *peripheral* mechanism for the force-related errors. Central sources of error will be evaluated below.

Contributions of Different Muscle Afferents: Isometric versus Isotonic States

During isometric contraction, existing evidence suggests that all three major muscle afferent systems are strongly activated (Vallbo, 1974). However, primary and secondary ending discharge may show much more modest rate increases or may even saturate at the higher levels of muscle force, given that the predominant increase in rate (as illustrated in Vallbo's 1974 isometric study) appears to occur at very low muscle forces (Vallbo, 1974). This observation was not noted explicitly by

Vallbo; however, all the published records of afferent fibre discharge in his study show an upward convexity of the rate versus torque relations. Furthermore, similar rate-torque relations are implied by observations published more recently (Burke, Hagbarth and Lofstedt, 1978), in which the EMG continues to increase over a greater range of force than the spindle receptor response (*see* fig. 3A in Burke *et al.*, 1978). There is also limited supporting evidence provided by recordings of gamma motoneuronal discharge in the primate trigeminal motor nucleus (Lund, Smith, Sessle and Murakami, 1979). In contrast, tendon organ discharge would probably continue to increase progressively with increasing isometric muscle force (Houk, Crago and Rymer, 1980). The net result is that, under isometric conditions, tendon organ discharge is probably the only muscle afferent signal whose firing rate is likely to be proportional to muscle force over a wide range of operating conditions.

During isotonic flexor muscle shortening, spindle receptor discharge would be expected to diminish and tendon organ discharge to remain approximately constant. It appears that a maintained and unilateral elevation of tendon organ discharge is most likely to occur in isometric states, which is precisely when the positional errors arise.

Muscle Vibration

The observation of increasing flexion error with increasing isometric force was quite contrary to what we had expected on the basis of the vibration illusion (Goodwin *et al.*, 1972*a*; Eklund, 1972). Vibration of an isometric muscle produces a sense of muscle extension (Goodwin *et al.*, 1972*a*), which has been attributed to the activation of primary muscle spindle receptors (although both secondary and tendon organ afferent discharge may also be increased to some degree (Brown, Engberg and Matthews, 1967; Burke *et al.*, 1976). In brief, the hypothesis suggests that the vibratory stimulus induces a level of Ia afferent excitation which the nervous system would normally associate with a substantial (perhaps continuing) increase in muscle length. In our present experiments, increasing isometric muscle force, which we presume to be associated with a fusimotor-induced increase in Ia afferent discharge, is accompanied by the opposite illusion, that of muscle shortening. It is instructive to further compare the vibration studies with the results of our present experiments.

For example, Goodwin *et al.* (1972*a*) showed that vibration of human elbow flexors (biceps brachialis) did not induce a strong sensation of elbow extension until the joint flexion which accompanied the tonic vibration reflex was arrested, and the elbow flexors began to develop isometric force. However, if the isometric force was very high (induced by either a strong tonic vibratory response or by added voluntary force), then the vibratory illusion subsided. Similar observations were reported by McCloskey (1973), who found that the velocity of the motion perceived during vibration diminished as the magnitude of the load supported by the muscle was increased. The above authors have suggested that the illusion declines with increasing force, because the muscle spindle afferent discharge achieved during vibration reaches rates equivalent to those recorded during isometric muscle contraction, that is, the discharge rates are now appropriate for the muscle state. However, if Vallbo's (1974) observations may be extrapolated to elbow musculature, then spindle receptor discharge may not continue to increase as hypothesized.

As an alternative, we would suggest that illusions of position and motion are most evident in the isometric state because muscle force and length are temporally uncoupled—increasing force producing no significant length change under these conditions. This uncoupling of these variables permits 'anomalous' relations to be established between muscle force and length, or more explicitly, between the muscle afferent signals relating to these variables. The nature of the anomaly will be addressed further in the next section. Second, it is also hypothesized that the increasing isometric force produced during both vibration and voluntary contraction negates the excitatory effect of the increased Ia input (evoked by either tendon vibration or fusimotor activation). This negation, which could be produced by force-related inhibition of some spindle afferent-activated neuron, would produce a sensation akin to muscle shortening.

Physiological Basis of Isometric Error: an Efference Copy Hypothesis

Although it appears that spindle and tendon receptors may contribute to the sense of joint position, the differences between isometric and isotonic states still require explanation. It seems unlikely that the isometric errors originate in any specific combination of instantaneous static muscle force and length, because most physically attainable combinations of these variables can probably be established under either isotonic or isometric conditions. Moreover, force and length-related afferent signals can probably achieve similar combinations of discharge rates in either state. The difference may be that the 'path' or sequence of change in the afferent signals is not comparable in isometric and isotonic states, that is, errors could arise out of the differences in the temporal properties of the afferent input. By definition, isometric force does not give rise to any external motion; therefore it is possible that it is this lack of movement which produces the temporal patterns of muscle afferent discharge that give rise to the illusion. It is proposed that errors arise from a mismatch of *afferent* force and length information with a central model or reference, derived in turn from efference copy information. Such a scheme is to be distinguished from models which rely solely upon *efferent* command. The latter approach appears to have little current support (cf. Goodwin *et al.*, 1972*a*; McCloskey and Torda, 1975; Roland and Ladegaard-Pedersen, 1977; Matthews, 1977).

To summarize our scheme briefly, the essential point is that, for any given set of initial conditions (that is, of joint torque and angle), the nervous system normally expects a muscle under voluntary control to follow a specified trajectory, or 'load path' relating force and length. This 'load path' is no more than a specific formulation of an 'efference copy' hypothesis, requiring that the central reference level varies systematically in time. Information regarding the actual variations in muscle force and length is derived from spindle and tendon organ afferent discharge respectively. For agonist muscles undergoing voluntary shortening, such a path would be accompanied by declining spindle afferent discharge, and relatively constant tendon organ discharge. In the isometric state it is suggested that force and length information is misinterpreted, because tendon organ discharge is now increasing in the face of essentially constant spindle receptor afferent discharge, an anomalous combination of signals.

It is also proposed that the computation of the force and length 'path' may use excitatory projections from spindle afferents, and inhibitory projections from Ib interneurons, converging upon some neuron or neuronal group. This type of convergence would account for the opposed effects of isometric force and vibration, and it also suggests that some function of force and length, such as stiffness (or compliance) is being computed; a calculation reminiscent of that which may be required for the proposed regulation of muscle stiffness (*see* Nichols and Houk, 1976).

The above scheme can accommodate many of the current observations on the interactions between force and joint position sense. For example, the gamma-based spindle receptor activation that accompanies the transition from passive to active movement (which presumably occurred in our isotonic study) does not induce error, because it is effectively counterbalanced by the central actions of increasing tendon organ afferent input. Moreover, the sense of movement and positional change that accompanies vibration arises because spindle receptor activation occurs without appropriate or coherent force-related data. In the same vein, increasing isometric force inhibits the vibratory illusion because the tension signal approaches a value appropriate for the level of primary spindle ending discharge.

To this point, we have mounted a circumstantial case supporting a tendon organ contribution to our isometric errors; however, other sources of force-related information (not necessarily peripheral in origin) also warrant brief consideration.

Central Sources of Force-related Information

Force-related information could be provided by a separate sense of effort (McCloskey, 1973; Gandevia and McCloskey, 1977*a*, *b*) which might well co-exist with a sense estimating peripheral force directly.The relative importance of these two contributions (effort and force) can be readily distinguished, because a sense of effort would probably increase with fatigue or other physical weakness, whereas a force-related signal would remain constant or perhaps decline under similar conditions. As we have described in our experiments, the errors appeared better correlated with operating force than subjective effort.

Given the lack of clear support for other sources of force-related information, a tendon organ contribution remains plausible. Furthermore, spinal segmental Ib projections are well established (Eccles, Eccles and Lundberg, 1957), and supraspinal projections are probable. Whatever the site of any computation processing length and force-related information, the net calculation appears to associate increasing spindle receptor discharge with greater muscle length, and force-related discharge (presumably resulting from tendon organ discharge) with shorter muscle length. Such actions are also consistent with known excitatory and inhibitory actions of muscle afferent projections to homonymous motoneurons.

It is also apparent that this approach to the recognition of limb position incorporates signals derived from several types of muscle afferents, implying that joint position may be computed, or estimated, from a range of afferent information, rather than sensed directly, as appears to be the case for many other types of somatic sensation.

Position Sense in Passive Limbs

Although tendon organ input may contribute to position sense, it is clearly not an obligatory component since position sense persists in the passive or paralysed limb. We would suggest that isolated spindle input, derived from the passive limb, defines the limit of a possible range of force-length relations, the other limit being the isometric state, in which strong motor activity induces no external movement.

SUMMARY

The effects of isometric and isotonic force production on perceived static joint position were investigated in 12 adult subjects. The joint examined was the proximal interphalangeal joint of one index finger, and its perceived position was determined from matching movements of the equivalent joint on the other hand. When the perturbed joint was free to move, even when supporting substantial loads, the position was accurately estimated; however, when the subject was required to exert substantial isometric force against the device imposing the joint movement, significant errors occurred: these errors were in the direction of the increasing force. Similar effects were evident during increasing isometric flexion force in anæsthetized fingers.

It is suggested that force-related afferent discharge from muscle, presumably originating in tendon organ receptors, contributes to static joint position sense. This force-feedback may allow the nervous system to accommodate for the effects of changing fusimotor bias, but it also appears to induce errors when afferent information of force and length provide potentially conflicting information.

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BRAIN CONTROL OF CONJUGATE HORIZONTAL AND VERTICAL EYE MOVEMENTS

A SURVEY OF THE STRUCTURAL AND FUNCTIONAL CORRELATES

by MORRIS B. BENDER

(*From the Department of Neurology, Mount Sinai School of Medicine, New York, New York 10029*)

INTRODUCTION

THE neuroanatomical basis for conjugate eye movements in the horizontal, vertical, or oblique planes has never been clearly demonstrated. Fibre pathways transmitting impulses for such movements have been thought to be part of 'corticofugal or corticobulbar' pathways with 'connections between visual, frontal and brain-stem structures'. Our knowledge of these pathways has been derived primarily from clinicopathological studies of patients with paralysis of eye movements, from effects of electrical stimulation and lesion at different levels of the cerebrum and brain-stem and most recently from electrophysiological studies.

Historically, impairment of lateral movements of the eyes to one side associated with ipsilateral hemiplegia had been generally known for some time but the earliest case report was by Andral in 1834. Paralysis of conjugate gaze with a contralateral hemiplegia was first described by A. Foville in 1858. Without benefit of post-mortem examination, Foville postulated a 'centre' for horizontal gaze in the pons. Subsequently, two types of horizontal gaze palsies were recognized. The patient 'looks away from hemiplegia' in a cerebral lesion and 'toward the hemiplegia' in a pontine lesion (Prevost, 1868). These two clinical entities suggested that the corticofugal pathways transmitting eye movements in a contralateral direction must cross in the brain-stem. There was discussion of a specific decussation of fibres transmitting facial movements (Gubler, 1856), but there was none for ocular gaze. The decussation theory which surfaced at the beginning of the nineteenth century (Yelloly, 1808; M. Foville, 1844) was overshadowed by the concept of 'centres' which then dominated neurological thinking. According to this model, higher 'centres' for contralateral horizontal gaze were roughly situated in the occipital, parietal or frontal lobe cortex and a lower 'centre' for ipsilateral gaze was localized within the pontine tegmentum near the abducens nucleus (Wernicke, 1877).

As for vertical gaze the first description of paralysis for 'upward' movement was by Henoch in 1864, for 'upward and downward' gaze by Wernicke (1876) and for 'downward gaze' by Gee (1890). Each of these case reports included gross autopsy findings and the responsible lesion was usually a large tuberculoma located in the 'quadrigeminal region'. Parinaud (1883), an ophthalmologist in Charcot's clinic, described the syndrome of difficulty in upward and downward gaze without reference to post-mortem examinations. Later, he realized that the syndrome was caused by a lesion in the quadrigeminal plate (Parinaud, 1886) and still later, he thought that the 'centre for vertical gaze' was situated in the frontal lobe (Parinaud, 1892). This notion was in accord with the conclusions of Munk (1890) and Mott and Schaefer (1890) whose stimulation experiments in dogs and monkeys led them to postulate that the inferior part of the 'frontal eye centre' controlled upward movements of the eyes and the superior part controlled binocular downward movements. In their scheme the intervening portion controlled associated lateral movements.

Parinaud's localization for vertical eye movements was challenged by Spiller (1905) who reviewed the French, German and English literature and concluded that the lesions responsible for vertical gaze palsies were situated in the vicinity of the 'aqueduct of Sylvius'. In general, the case descriptions were sketchy, the pathological lesions were gross, extending over many critical areas in the brain and there were few, if any, significant histological examinations. Despite these inaccuracies clinicians continued to believe that localization of normal oculomotor functions was provided by the study of brain lesions causing defects in ocular gaze. With this in mind they prodded the experimentalist to search for a 'physiological' interpretation of eye movements.

It was known that an 'irritative' lesion of the cerebrum resulted in a contralateral horizontal or oblique 'associated eye movement' (Jackson, 1866, 1870). However, precise localization of the lesion which caused a particular defect in movement could not be ascertained without comparative investigations in experimental animals. About that time researches on the excitability of the cerebral cortex in the monkey and other animals were begun (Adamük, 1870). It was found that electrical stimulation of the cerebral cortex evoked body and eye movement. The eyes almost always moved conjugately to the contralateral side (Ferrier, 1875; Schaefer, 1888; Risien Russell, 1894). Subsequently, the effects of electrical stimulation of subcortical regions were studied (Beevor and Horsley, 1890). Systematic investigations of electrical stimulation of the brain in man was initiated much later (Foerster, 1931, 1936; Penfield and Boldrey, 1937). These neurosurgeons found that eye movements in man could be elicited not only from the frontal or occipital lobes but from widespread regions of the cerebral cortex. With the innovation of the stereotaxic instrument in the first quarter of this century, electrical stimulation and discrete focal lesioning in the brain-stem provided more precise additional information (Horsley and Clarke, 1908; Hess, 1932; Ingram, Ranson, Harnett, Zeiss and Terwilliger, 1932). Following these studies and the pioneer investigations of Lorente de Nó (1933), there ensued the modern era of electrophysiological and later neuroanatomical tracer studies of the oculomotor system. It should be noted that clinicians of the nineteenth and early twentieth century anticipated some of the recent electrophysiological discoveries, for example, the role of the abducens nucleus and the median longitudinal fasciculus in conjugate gaze (A. Foville, 1858; Von Monakow, 1897). Generally, texts and reviews tended to assign specific functions to specific areas of the cerebrum and brain-stem and then proceeded to stress pathways connecting these 'centres'. But morphological as well as physiological evidence for these presumed pathways was often incomplete. Equally important, haste in assigning specific functions to specific areas or 'centres' has often caused neuroscientists and clinical neurologists to overlook many aspects of the over-all organization of the oculomotor system.

The purpose of the present communication is to review the anatomical and physiological organization of oculomotor functions within the brain with particular emphasis as to *direction* of conjugate eye movements, derived from experimental data collected during the past forty years. Identification of pathways which transmit signals for conjugate eye movement in the horizontal and vertical planes were conducted by three principal methods: (a) unilateral and bilateral electrical stimulations; (b) unilateral and bilateral localized lesioning; and (c) by electrical recordings from cells within the cerebrum and brain-stem of the monkey. Whenever possible, these animal experiments were correlated with those conducted in earlier years and with clinicopathological studies in man. In addition, newer anatomical studies using antero- and retrograde autoradiographic and amino acid tracer techniques, as summarized by Graybiel (1977*a*) were correlated with the electrophysiological data obtained in animals (Raphan and Cohen, 1978). There will be some repetition in this approach but to the extent that different techniques corroborate or complement one another, some details of the fine structure of the oculomotor system will emerge. It will be emphasized in what follows that a remarkably consistent mapping of eye movements is maintained throughout the brain. This parallels the clear mapping of afferent inputs from visual space into the calcarine cortex.

EFFECTS OF STIMULATION WITHIN THE OCULOMOTOR SYSTEM

(1) *Horizontal Eye Movements on Unilateral Stimulations*

At a symposium on the oculomotor system held in 1961, we summarized our observations on the effects of unilateral focal electrical stimulation or lesion of the brain in regard to all types of conjugate eye movements in alert and anæsthetized monkeys. Unilateral electrical stimulation of the cerebrum of the normal monkey evoked a binocular horizontal tracking movement, almost invariably in a contralateral direction, whether the stimulation was cortical or subcortical in the frontal, parietal, temporal or occipital lobes. As a rule, the contralateral binocular deviations were horizontal but almost as frequently oblique. Contralateral horizontal or oblique eye movements were obtained from stimulations of individual loci over most of the entire cortex and subcortex, especially the occipital and frontal lobes (Wagman, Krieger and Bender, 1958). Purely vertical (up or down) movements were rarely obtained (fig. 1). The direction of the conjugate eye movements was invariably contralateral when the stimulations in the brain were above the level of the oculomotor-trochlear nuclei. Unilateral stimulation within the diencephalon or the mesencephalic reticular formation resulted in contralateral horizontal or oblique gaze with a minimal latency of 20 ms (Komatsuzaki, Alpert, Harris and Cohen, 1972). Below the midbrain level, unilateral stimulation of the paramedian pontine reticular formation resulted in ipsilateral horizontal binocular deviation.

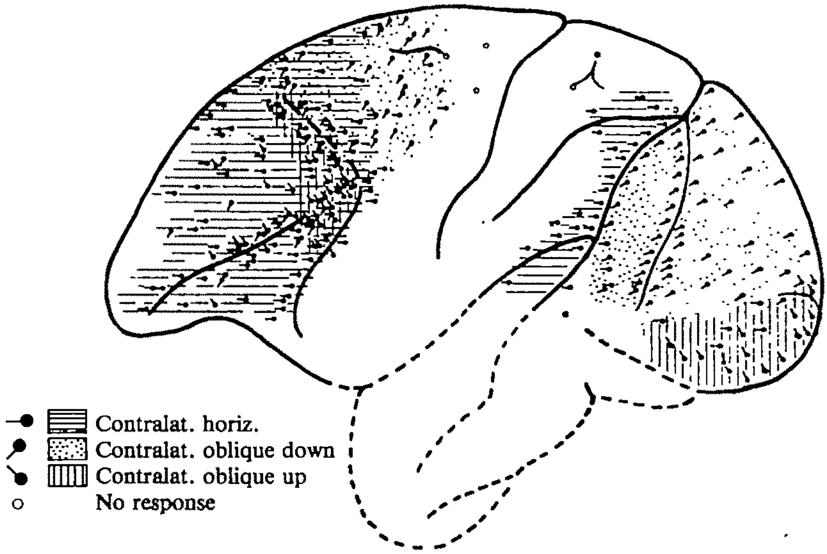

FIG. 1. Conjugate eye movements elicited upon stimulation of the cerebral cortex of the alert, cervically transected monkey. The portion outlined by the broken line, which includes most of the temporal lobe, was not explored in detail. This schematic diagram summarizes the data obtained on 16 monkeys. Each solid circle represents a responsive point. The line originating at a circle indicates the direction of movement, either horizontal, vertical, downward oblique or upward oblique. No ipsilateral deviations were obtained. A hypothetical plane formed by the two calcarine fissures, and which extends laterally to the surface of the occipital lobes, divides the downward (dotted) from upward (vertical lines) oblique responses (Wagman *et al.*, 1958).

It should be emphasized that the conjugate eye movements elicited by stimulation of the cerebral cortex were not necessarily a primary oculomotor effect. In many instances it may have resulted from excitation of a sensory system localized within the occipital, parietal or temporal lobes which ultimately reaches the oculomotor system, as discussed by Schaefer (1888) and Munk (1890). There are two classes of binocular movements: (a) quick or saccadic and (b) slow or tracking. Although saccadic and tracking movements may serve different purposes, they do not occur independently. Saccades control the onset, duration and location of tracking movements. The supranuclear optomotor regulation occurs mainly in mechanisms of the pons and mesencephalon, aided by neuronal subsystems of the cerebral cortex, the diencephalon and cerebellum (Jung, 1972).

Stimulations within the pons. The latency of the electrically-induced binocular movement in the pons (or below the oculomotor decussation) was short (3 ms), indicating that few synapses are interposed between the nuclei situated within the paramedian pontine reticular formation and the eye motor nuclei. The area of the electrically excitable paramedian pontine reticular formation extended from the midline, laterally for 2 to 3 mm and rostrocaudally from the oculomotor nuclei to the level of the abducens and vestibular nuclei (Cohen and Komatsuzaki, 1972). Stimulations at the level of the abducens nucleus resulted in abduction of the ipsilateral eye. When the electrode was more ventrally situated, that is, near the paramedian zone, there was ipsilateral deviation of both eyes (Bender and Shanzer, 1964). Further investigations disclosed that electrical stimulation of the vestibular nuclei and their connections, including the cerebellum, also resulted in conjugate eye movements (Cohen, 1974).

The foregoing observations indicate that oculomotor pathways subserving contralateral conjugate gaze extend from the cerebrum to the oculomotor-trochlear nuclei at which level these pathways presumably cross and project to the pontine tegmentum (Monnier, 1946; Hess, Burgi and Bucher, 1946; Bender, 1962). Though there is no compact dense decussation like the optic chiasma or the decussation of the pyramidal tracts, there is clear proof of a crossing of pathways across the midsagittal plane, as derived from electrical stimulations and electrolytic lesion studies in animals. According to Phillips and Porter (1977) the evidence for such a crossing might be designated 'electroanatomical'.

Most oculoversions are associated with head turning, the eyes preceding the head by a fraction of a second. During eye and head turning overt movements of the eyes precede those of the neck. However, electromyographic recordings indicate activity within the external rectus 20 ms after that of the neck muscles (Bizzi, Kalil and Tagliasco, 1971).

'Electroanatomical' evidence for a decussation of pathways mediating head turning was also found. Both binocular and head turning were contraversive when the electrical stimulations were above the oculomotor decussation. Below this level, unilateral stimulations of the pontine reticular formation resulted in dissociation between the eye and head movements; the conjugate eye deviations became ipsilateral, whereas the head-chin turnings remained contralateral. The area for dissociation between eyes and head extended for a distance of 3 to 4 mm below the oculomotor decussation. Caudal to this level unilateral stimulations of the paramedian pontine reticular formation evoked both head and eye movements to the ipsilateral side. Evidently, an 'electroanatomical' cephalomotor decussation is situated in the lower pons or 3 to 4 mm caudal to the oculomotor crossing in the midbrain (Bender, Shanzer and Wagman, 1964).

(2) *Vertical Eye Movements*

(a) *Unilateral stimulations.* As for conjugate eye movements in the vertical plane, unilateral electrical stimulation experiments were inconclusive. The frequent incidence of oblique movements suggested the existence of a vertical component in addition to the omnipresent and usually the more 'powerful' horizontal vector. Following unilateral stimulation within the cerebrum the direction of the horizontal binocular movement was invariably contralateral, whereas the direction of the vertical component of the oblique response, whether upward or downward, depended upon the site of stimulation. Contralateral oblique binocular movements with a downward component were obtained from stimulations of the more dorsal regions of the occipital lobe or from areas situated above a hypothetical horizontal plane formed by the two calcarine fissures (Wagman, 1964). Conversely, contralateral obliquely upward eye movements were elicited from stimulations of the ventral regions or at levels below this 'calcarine' hypothetical plane (Wagman *et al.*, 1958) (fig. 1). The vertical component (up or down) of the oblique response was also obtained but less consistently on unilateral stimulations of the frontal, parietal or temporal lobes (Wagman, Krieger, Papatheodorou and Bender, 1961). In general, the direction of the vertical component of the binocular oblique action, obtained on unilateral electrical stimulation throughout the brain, was related to this hypothetical transverse or horizontal plane defined by the right and left calcarine cortex (Papatheodorou, Wagman, Krieger and Bender, 1956; Krieger and Bender, 1957). Purely vertical conjugate eye movements on unilateral stimulations within the cerebrum were rare. Occasional direct up or down binocular movements were obtained on unilateral stimulation in the occipital lobe, in the midline of either the diencephalon, mesencephalon, or the pontine tegmentum of the monkey (Bender and Shanzer, 1964; Kömpf, Pasik, Pasik and Bender, 1979). Binocular movements strictly in the vertical plane have also been elicited in man on unilateral electrical stimulations within the diencephalon near the midline or laterally as far as 13 mm from the midline (Spiegel, Wycis, Szekely, Soloff, Adams, Gildenberg and Zones, 1964; Nashold and Gills, 1967).

(b) *Bilateral stimulations.* Purely vertical responses were consistently obtained on bilateral simultaneous stimulations of the cerebrum and lower structures. Simultaneous electrical stimulations of homotopic loci in the superior half of each occipital lobe above the hypothetical transverse plane resulted in straight downward eye movements, whereas stimulations of the inferior halves yielded directly upward movements (Schaefer, 1888; T. Pasik and P. Pasik, 1964). Simultaneous stimulations of the frontal lobes produced straight upward or downward binocular movements; stimulations of the more superior portions yielded downward, while the inferior regions yielded upward binocular movements (Mott and Schaefer, 1890). Similarly, bilateral simultaneous stimulations of the cerebellum evoked prompt upward or downward movements; the direction depended upon the location of the stimuli (Cohen, Goto, Shanzer and Weiss, 1965). There was no demonstrable region in the cerebellum which indicated a separation between the up and down movement as found in the cerebrum.

Bilateral electrical stimulations within the diencephalon and mesencephalon zone yielded binocular movements which were exclusively in the vertical plane. This zone which extends on both sides from the thalamus down to the oculomotor nucleus and 6 mm laterally from the midline includes parts of the thalamus, fields of Forel, zona incerta, the subthalamic nucleus, the red nucleus, fasciculus retroflexus and other adjacent structures at this level. More caudally to the mesodiencephalic plane the zone includes the mesencephalic reticular formation, oral portions of the nu. oculomotorius, rostral portions of the median longitudinal fasciculus, posterior commissure and the pretectum. Unilateral electrical stimulation within most of these regions induced a binocular movement to the opposite side except at the level of the nu. oculomotorius where the responses became monocular. With unilateral stimulation there were either vertical or contralateral oblique movements; horizontal deviations could be elicited in more lateral regions. With bilateral stimulations within the diencephalon there ensued straight downward movements. More caudally at the level of the mesencephalon the vertical movements changed to an upward direction. The demarcation between the two regions was close. The upward deviations were obtained 1 to 2 mm ventrally and medially to the area which yielded downward gaze. The electrically-induced binocular upward movements were not as strong as the more dorsally situated stimuli which yielded downward movements (Kömpf *et al.*, 1979).

From the foregoing there appeared to be another hypothetical transverse plane within the diencephalomesencephalic region which separates the up-down binocular movements. This transverse plane is similar to the separation noted within the cerebrum, especially in the occipital lobe. Evidently, the relationship of down-up vectors was maintained within the pathways coursing from the cerebrum down to the diencephalomesencephalic region with ultimate projection to each oculomotor nucleus (fig. 2). There was no evidence of a decussation of these pathways (mediating up and down gaze) across the hypothetical transverse plane, as found between the pathways transmitting right and left horizontal gaze across the midsagittal plane in the midbrain. In this connection it should be pointed out that a similar organization is present in the visual system. There is no decussation between optic pathways which transmit impulses through the superior and inferior altitudinal halves of the retino-geniculate calcarine pathways but only between the right and left half fields across the midsagittal plane at the optic chiasma.

Bilateral simultaneous stimulations of sensory systems also evoked eye movements in the vertical plane. Bilateral thermokinetic stimulations of the semicircular canals induce excellent vertical eye movements in man and monkey (Bender, 1960).

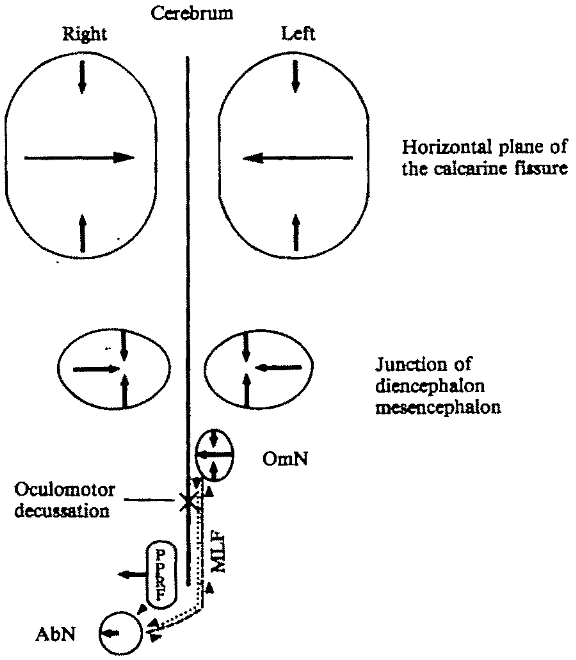
Cerebrum
Right
Left
Horizontal plane of the calcarine fissure
Junction of diencephalon mesencephalon
OmN
Oculomotor decussation
PPRF
MLF
AbN

FIG. 2. Diagram illustrating principal direction of binocular movements within the brain and monocular movement within the oculomotor nucleus (OmN) in terms of vectors. Arrows indicate direction of vector action in the horizontal and vertical planes. The degrees of oblique actions which varied with the sum of horizontal and vertical vectors are not indicated. In the cerebrum and OmN the horizontal vector was the most powerful. Arrow heads indicate direction of transmission of impulses from the paramedian pontine reticular formation (PPRF) to the ipsilateral abducens nucleus (AbN) and to the opposite median longitudinal fasciculus (MLF) (dash lines) ascending to motoneurons of the medial rectus within the OmN. Other arrow heads indicate direction of impulses transmitted downward through the same MLF (dotted lines) to the AbN.

The same can be obtained on bilateral electrical stimulations of semicircular canal nerves with implanted electrodes in the monkey and cat (Cohen, Suzuki and Bender, 1964). More specifically, simultaneous electrical stimulations of the two anterior canals yield upward movements, while the two posterior canals result in pure downward binocular movements. Oblique eye movements can be obtained by stimulating a combination of either the anterior or posterior with the lateral canal (Cohen, Tokumasu and Goto, 1966; Suzuki and Cohen, 1964).

There is a continual resting discharge of impulses flowing from the semicircular canals into the oculomotor system, thus constantly influencing oculomotor tone (Lowenstein, 1950). It is conceivable that the semicircular canals begin to generate impulses for oculomotor activity (vestibulo-ocular reactions) early in fœtal life. Subsequently, the component of the vector pattern derived from each canal becomes embedded or imprinted within the oculomotor pathway. At birth the vestibulo-ocular reflex is almost complete. In later life, during infancy when visual inputs appear, visuo-oculomotor pathways are similarly developed so that vectors for vergence, optic fixation and other co-ordinate movement of the eyes can be identified.

Bilateral visual stimulations of the cerebral hemisphere are essential to evoke truly vertical eye movements. Visual stimuli, moving in the vertical plane before the eyes of alert man or monkey, result in vertical optokinetic nystagmus provided both halves of the visual system are stimulated in one or both eyes. If only one of the cerebral hemispheres is so stimulated, such as in a split-brain preparation with section of the corpus callosum and optic chiasma, the vertical optokinetic nystagmus elicited on monocular stimulation will be defective with resultant contralateral oblique nystagmus (T. Pasik and P. Pasik, 1964; Pasik, Pasik, Valciukas and Bender, 1971).

In a split-brain preparation with section of the corpus callosum and optic chiasma, visual (optokinetic) stimuli moving toward the nasally blind retina will not evoke a saccadic response. On the other hand, optokinetic stimuli moving horizontally in the direction of the seeing or temporal retina will result in a contralateral horizontal saccadic movement. Purely upward or downward optokinetic nystagmus cannot be elicited when either eye is visually stimulated in the vertical plane. Instead, there is an oblique contralateral optokinetic nystagmus or a sum both of the vertical and the predominant horizontal vectors elicited by the seeing temporal retina. When the right and left eye are stimulated simultaneously, then both cerebral hemispheres of the split brain are activated simultaneously by the right and left temporal retina and optokinetic nystagmus can be elicited either in the horizontal, vertical or oblique planes depending upon the direction of the moving visual stimuli. Thus, true vertical movements occur only when the right and left oculomotor pathways are activated through bilateral sensory inputs. The direction of eye movements, whether up or down, depends upon the origin of the sensory inputs. When the visual stimuli are directed upward, then saccades move down and when the visual stimuli move downward, the nystagmus is upward.

(3) *Unilateral Stimulations at the Level of the Oculomotor Nucleus*

Whereas unilateral stimulations above the level of the oculomotor nucleus, for example, in the mesencephalic reticular formation, induced binocular movement in a contralateral direction and stimulations below this level in an ipsilateral direction, electrical stimulation along the border or in the region of the oculomotor nucleus resulted in monocular movements of the ipsilateral eye (Bender and Weinstein, 1942). The direction of the monocular movement varied with the site of the electrode along the dorso-ventral or rostro-caudal co-ordinates. Stimulation at the oral pole of the nucleus resulted in downward movement of the ipsilateral eye. As the electrode was advanced at 0.5 mm intervals toward the inferior pole, the direction of the eye movement changed to obliquely downward. When the stimulating electrode reached the median point, between the two poles of the nucleus, the direction became horizontal and inward. Below the median point the movement changed to obliquely upward and at the inferior pole the movement became directly upward. As shown in Table 1, the adduction of the ipsilateral eye was horizontal and in a contralateral direction. The direction of the horizontal vector of the oblique movements was also contralateral.

TABLE 1. MONOCULAR MOVEMENTS OBTAINED ON ELECTRICAL STIMULATION IN REGION OF THE LEFT OCULOMOTOR NUCLEUS AND ITS ROOTLETS ALONG VERTICAL (DORSO-VENTRAL) AND HORIZONTAL (ROSTRO-CAUDAL) CO-ORDINATES WITHIN THE BRAIN-STEM

Polar co-ordinates	*Direction of monocular movement*
Rostral or dorsal	Downward
	Downward and inward (contralateral obliquely downward)
	Inward (contralateral horizontal)
	Upward and inward (contralateral obliquely upward)
Caudal or ventral	Upward

The direction of monocular movement obtained on electrical stimulation of the left OmN changed as the electrode descended at 0.5 or 1 mm intervals. At the oral pole the movement was straight down and one might conclude it was effected by contraction of the inferior rectus muscle. At slightly lower level of the OmN, the movement turned slightly inward and here there must have been a combination of inferior and internal rectus actions. As the electrode descended, the angle of the motor response changed until there was true horizontal internal deviation, probably due to action of the medial rectus. Below this level the response again became oblique but the action had an upward component. The obliquity increased as the electrode descended to the inferior pole of the OmN when the monocular movement became straight upward and the muscle responsible for this action is presumed to be the superior rectus.

This changing pattern was also obtained when the stimulating electrode was advanced through the region of the oculomotor nucleus along horizontal co-ordinates, i.e. in a rostro-caudal or caudo-rostral direction. Stimulation of the most caudal region of the oculomotor nucleus resulted in upward, while the most rostral portion resulted in a downward monocular movement. The direction of the ipsilateral monocular movements elicited by stimulation suggested that the arrangement of ocular muscles represented within the third nerve nucleus of the monkey is that the inferior rectus is in the most oral and the superior rectus in the caudal region of the nucleus (Bender and Weinstein, 1943). This was comparable to the arrangement of eye muscles represented in this nucleus found in stimulation experiments of other animals, dog (Danis, 1948) and cat (Szentágothai, 1942). The organization of the motor neurons within the oculomotor nucleus, namely, (a) cells innervating the inferior rectus being situated in the rostral and (b) cells innervating the superior rectus in the caudal region, was roughly similar to the topography determined by retrograde degeneration studies (Warwick, 1953, 1964) and by horseradish perioxidase techniques (Gacek, 1974). Finally, it should be noted that the organization of monocular movement activated by its ipsilateral oculomotor nucleus is similar to the organization of binocular movements when the supranuclear pathways were activated (Kõmpf *et al.*, 1979). The topographic arrangement for vertical movement in each instance was such that the impulses for downward gaze were transmitted through more dorsal and rostral regions of the brain, while those for upward were through the ventral or caudal regions.

(4) *Eye Movements and Vectors*

It is known that during a conjugate movement no single eye muscle acts alone. It is also probable that no single or group of cells or fibre pathways transmit impulses for a particular conjugate gaze. There are no known specific pathways which subserve only horizontal, vertical or oblique binocular movements, except possibly within the brain-stem. Although parts of the neural mechanism for horizontal and vertical gaze are separate in the brain-stem, there is fragmentary evidence that all rapid eye movements may originate in a single region of the paramedian pontine reticular formation (Raphan and Cohen, 1978). In every binocular movement groups of muscles contract, while others relax by reciprocal innervation. In this manner, graded movements of great delicacy are executed by an interplay of excitatory and inhibitory units. Such integrated motions are controlled by a series of excitatory and inhibitory impulses flowing from the cerebrum *via* yet unidentified corticobulbar pathways and modified by a variety of sensory inputs.

These programmed impulses for eye movements, whatever the origin, may be conveniently expressed in terms of vectors (Henn and Cohen, 1972; Büttner, Hepp and Henn, 1977). Each binocular movement is a vector quantity with an amplitude and direction which within a biological system can not be measured, but only observed by its effects. Each movement can be characterized as a sum of displacement along a horizontal and vertical axis. The predominant response on unilateral stimulation is a horizontal displacement and, at times, with a vertical component (oblique movement). The vertical vector (down or up) within one side of the brain is constantly modified by the horizontal which is the greater or more 'powerful' of the two (Jackson, 1894). When the two sides of the brain are simultaneously activated, the opposing right and left horizontal vectors cancel each other and the pure vertical vector (down or up) remains (fig. 2).

The vectors generated on the right side of the brain are in constant tonic equilibrium with those on the left. To execute a conjugate movement to the left, horizontal vectors are activated by the oculomotor units on the right side of the brain, while at the same time, units on the left are reciprocally inhibited. For an oblique movement, both horizontal and vertical vectors are integrated. For pure vertical movements the vertical vectors are activated on both sides of the brain, while the right and left horizontal vectors cancel each other and are in equilibrium.

As indicated above, the presence of the horizontal and vertical vectors can easily be identified by (a) electrical stimulations of the brain; (b) stimulations of the vestibular system, namely, individual semicircular canals; (c) by visual (optokinetic) stimulations in the split-brain preparation. Still another method of detecting the presence of a vertical vector, introduced in the nineteenth century, was that of unilateral cerebral stimulation, after paralysing the principal eye muscles involved in unilateral conjugate gaze (Risien Russell, 1894). This was suggested by Jackson (1894) who believed that whereas all types of eye movements were represented in the brain the most 'powerful' were those for contralateral deviation. Thus, on eliminating conjugate movement to the left by sectioning the left external and right internal rectus muscles, stimulation of the right cerebrum would evoke the remaining 'less powerful' movers. As predicted, right cerebral stimulation failed to move the eyes to the contralateral side. There were some ipsilateral binocular deviations but never true contralateral. Instead, the resultant movements unmasked the presence of vertical vectors, as manifested in contralaterally obliquely upward or downward deviations. The contralateral horizontal component of these oblique movements could not occur with denervated eye muscle and therefore, according to Sherrington (1893), must result from inhibition of ipsilateral vectors.

EFFECTS OF PARALYTIC LESIONS WITHIN THE OCULOMOTOR SYSTEM

(1) *Impairment of Horizontal Gaze Caused by Unilateral Lesions of the Brain above the Level of the Oculomotor Nucleus*

In general, lesions made at foci which on stimulation yielded binocular movement in a particular direction resulted in an impairment or paralysis of such movement, provided the lesion was sufficiently large (Bender and Shanzer, 1964). The degree and duration of the impairment of horizontal gaze varied with the size and location of the lesion. Selective extirpation of the cerebral cortex of the frontal or occipital lobe had little effect on spontaneous eye movement in the monkey (P. Pasik and T. Pasik, 1964). More massive unilateral decortications caused more distinct impairments of contralateral horizontal gaze. The more cerebral tissue damaged, the more enduring was the defect in spontaneous contralateral conjugate gaze. Hemidecortications on either side produced a paralysis of horizontal conjugate gaze to the opposite side which sometimes lasted several weeks but was never permanent. Although contralateral horizontal gaze was lost, vertical and ipsilateral oblique eye movements were preserved (Pasik, Pasik and Bender, 1960). Less massive cortical lesions produced less enduring impairment of contralateral conjugate eye movement. Also deeper subcortical lesions resulted in more prominent impairment of contralateral eye movements. The deeper the location of a given sized lesion the more damaging and enduring was the impairment of binocular gaze. Thus, a 5 mm electrolytic lesion in the region of the fields of Forel or zona incerta on the right produced a contralateral impairment of horizontal gaze to the left for forty-eight hours. Deeper in the mesencephalic reticular formation a smaller (2 to 4 mm) lesion on the right resulted in an even greater defect in eye movements to the left and which lasted longer (Komatsuzaki *et al.*, 1972) (Table 2).

TABLE 2. HORIZONTAL OCULOMOTOR RESPONSES ON UNILATERAL CALORIC STIMULATION OF ONE EAR CANAL IN AN ALERT MONKEY WITH A 2 TO 4 MM LESION IN THE LEFT DIENCEPHALON (ABOVE THE OCULOMOTOR DECUSSATION)

Caloric stimulus	*Ear stimulated*	*Direction of binocular movement*	
		Right vector	*Left vector*
Cold	Right	No tonic deviation to right	Nystagmus, fast component to left
Cold	Left	Defective nystagmus to right	Tonic deviation to left
Warm	Right	Defective nystagmus to right	Tonic deviation to left
Warm	Left	No tonic deviation to right	Nystagmus, fast component to left

(2) *Impairment of Horizontal Gaze due to Unilateral Lesions at the Pontine Level*

Below the level of the oculomotor-trochlear nuclei, still smaller (1 to 2 mm) lesions in the tegmentum of the pons, specifically in the paramedian pontine reticular formation, resulted in paralysis of ipsilateral conjugate gaze for as long as one year (Bender and Shanzer, 1964; Cohen, Komatsuzaki and Bender, 1968). This zone was less in extent than the electrically excitable region, which extended 5.0 mm from the trochlear to the abducens nucleus, 2.5 mm laterally from the midline and 2.0 mm ventrally. A 1 mm electrolytic lesion in any part of this smaller zone on the right side (fig. 3) abolished spontaneous or induced conjugate eye movements to the right (Goebel, Komatsuzaki, Bender and Cohen, 1971). Following such a focal lesion all types of horizontal eye movements were abolished, including both the saccadic and tracking movements of induced optokinetic and optokinetic after-nystagmus, as well as those induced by vestibular (caloric) stimulations (Table 3). It should be noted that the two principal types of conjugate eye movements, namely (a) tracking (smooth or tonic) and (b) patterned phasic saccades or nystagmus, were always ipsilaterally impaired by the lesions in the tegmentum of the pons. When recovery ensued, the spontaneous tracking movement recovered first. Later, there followed recovery of saccades of vestibular nystagmus, of optokinetic nystagmus and last to return were the saccades of after-nystagmus. Conversely, the loss of optokinetic after-nystagmus with preservation of other types of reflex eye movements was the first sign of deficits in oculomotor functions following lesion localized anywhere within the pathway, extending from the cerebrum down to the brain-stem (Shanzer, Teng, Krieger and Bender, 1958).

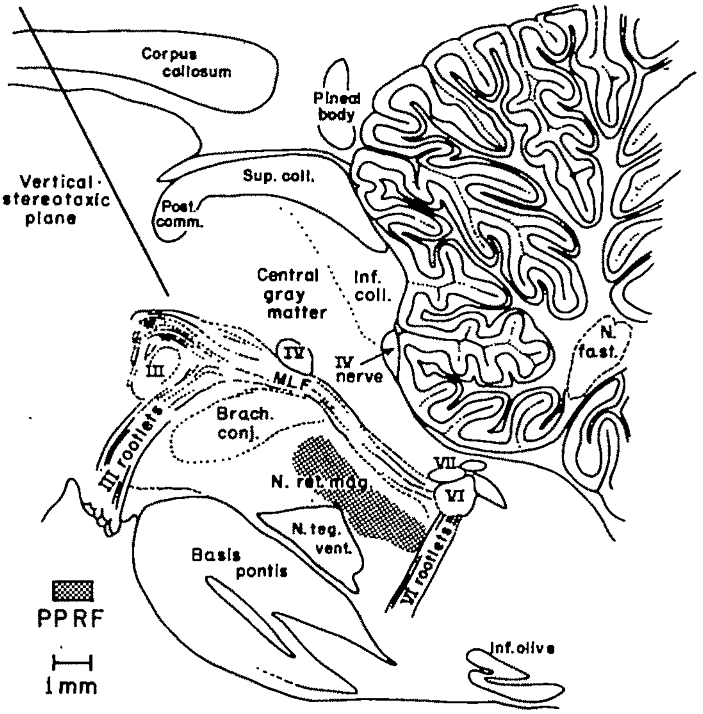

FIG. 3. Diagrammatic sagittal section of brain-stem 0.75 mm from midline. Solid line shows a vertical stereotactic co-ordinate. Checkered area shows extent of PPRF between levels of the trochlear and abducens nuclei, situated 2 mm ventrally to the MLF. A 1.0 mm lesion within any part of this zone caused paralysis of ipsilateral horizontal conjugate gaze. A 1.0 mm lesion within MLF caused impairment of contralateral horizontal gaze with paralysis of the adducting eye and instability (nystagmus) of the abducting eye. It should be noted that the electrically excitable zone was larger than the checkered area (Goebel *et al.*, 1971).

(3) *Lesions of the Abducens Nucleus*

Ever since A. Foville (1858) proposed the theory that the abducens nucleus was the 'lower centre' for horizontal conjugate gaze, there have been numerous clinicopathological and experimental studies which, according to Bruce (1903), firmly established this concept. Wernicke (1877), who made careful clinicopathological observations, confirmed Foville's hypothesis but made certain modifications which were subsequently accepted by many clinicians and pathologists (Hunnius, 1881; Van Gehuchten, 1904; Holmes, 1921; Freeman, 1922). Based on this hypothesis Wernicke (1877) and later Graux (1878) proposed that fibres emerge from a region 'ventral' to the abducens nucleus, cross the midline and ascend in the median longitudinal fasciculus, subsequently to interconnect with the opposite oculomotor nucleus. However, the pathway of transmission of impulses for horizontal conjugate eye movements was vague. Destruction of the nu. abducens as a rule causes paralysis of abduction of the ipsilateral eye but there have been reports of paralysis of ipsilateral conjugate gaze as well. Bennet and

TABLE 3. HORIZONTAL OCULOMOTOR RESPONSES ON UNILATERAL CALORIC STIMULATION OF ONE EAR CANAL IN AN ALERT MONKEY WITH 1 TO 2 MM LESION IN THE LEFT PARAMEDIAN PONTINE RETICULAR FORMATION (BELOW THE OCULOMOTOR DECUSSATION)

Caloric stimulus	*Ear stimulated*	*Direction of binocular movement*	
		Right vector	*Left vector*
Cold	Right	Marked tonic deviation to right	No nystagmus to the left
Warm	Right	Good nystagmus to the right	No tonic deviation to the left
Cold	Left	Good nystagmus to the right	No tonic deviation to the left
Warm	Left	Marked tonic deviation to the right	No nystagmus to the left

Savill (1889) and Carpenter, McMasters and Hanna (1963) found that the region ventral to this nucleus, sometimes known as the parabducens nucleus, was critical in the lesion responsible for the ipsilateral conjugate palsy.

The concept of the parabducens nucleus, a term introduced by Strong and Elwyn (1943), was popularized by Crosby (1953). She stated that 'in the reticular gray adjacent to the abducens nucleus and intermingled with the abducens neurons are small associative cells which constitute the parabducens nucleus'. Since then her belief that the parabducens nucleus was 'a center for horizontal eye movement' has been considered both anatomically and physiologically incorrect (Baker and McCrea, 1979). Furthermore, there were reports of paralysis of ipsilateral conjugate gaze caused by lesions outside of the abducens or the so-called 'parabducens' nucleus (Wernicke, 1877; Potts and Spiller, 1903) and, more specifically, in the ipsilateral paramedian pontine reticular formation (Monnier, 1946; Bender and Shanzer, 1964).

A. L. Foville's theory, which prevailed for over one-hundred years, was recently verified anatomically with retrograde tracer techniques by Graybiel and Hartweig (1974) and electrophysiologically by Baker and Highstein (1975) and Highstein (1977*a*, *b*). It was found that the abducens nucleus contains two types of cells, i.e. magnocellular motor neurons which innervate the ipsilateral external rectus muscle and other neurons which are not motoneurons but internuclear cells connecting the sixth with the opposite third nerve nucleus. Tsuchida (1906) showed anatomically a variety of cell sizes within the ocular nuclei but it was not clear whether these was a mixture of motoneurons and internuclear neurons, as proposed by Fuse (1912) and recently differentiated by electrophysiological techniques. The axons of these internuclear neurons emerge from the nu. abducens, cross the midline and ascend in the median longitudinal bundle to link with the motoneurons in the nu. oculomotorius, which innervate the opposite medial rectus muscle. From the most recent studies it appears that the nu. abducens contains cells which are important in generating ipsilateral ocular gaze (Baker, 1977*b*).

(4) *Combined Stimulation and Lesion Studies*

Following a unilateral lesion within the left paramedian zone of the pontine tegmentum, electrical stimulation of the right frontal lobe (arcuate cortex) failed to elicit the expected contralateral eye and head deviations to the left (Wagman, Shanzer and Bender, 1959). In some instances with stronger currents there occurred an ipsilateral eye-head deviation to the right. This ipsilateral response from cortical stimulation, which was never observed in the normal monkey, suggested the presence of an uncrossed pathway. Moreover, on stimulation of the right occipital lobe in the same preparation there occurred, after a longer latency, a 'weak', that is, a slow or incomplete conjugate deviation to the left; it required greater current for better or quicker and more complete binocular movements. These findings indicated that impulses from the cerebrum descend along pathways yet unknown and cross presumably to the opposite paramedian pontine reticular formation. Electrically induced impulses flowing from the arcuate cortex were blocked by a lesion in the opposite pontine reticular formation. Those induced from the occipital lobe were only partially blocked and required greater current to effect a contralateral gaze, as first observed by Mott and Schaefer (1890).

In summary, the above studies indicate that impulses for contralateral horizontal gaze are interrupted when the lesion is above the level of the 'oculomotor decussation' and for ipsilateral gaze when the lesion is below this level (Bender, 1960). There must be different corticofugal pathways subserving horizontal binocular movement which project from the frontal and occipital cortex toward the mesencephalon where these pathways decussate and also there may be another or uncrossed pathway. However, neither the hypothetically crossed nor uncrossed pathways transmitting impulses for horizontal deviations have been identified anatomically within the cerebrum. It had been suggested that the crossing fibres may be situated in the decussation of Meynert and project caudally in the tectospinal tract (Hess *et al.*, 1946). During the nineteenth century decussations of projections from the cerebrum to the cranial nuclei, especially to the facial, were thought to extend along the length of the brain-stem, down to the medulla (Gubler, 1856). To date, the exact connections between the corticofugal pathways and pontine tegmentum or the various ocular nuclei, are yet to be ascertained.

(5) *Lesions within the Median Longitudinal Fasciculus*

While electrical stimulation within the median longitudinal fasciculus of the monkey induced adduction of the ipsilateral eye, a 0.5 mm lesion at this point blocked such movement with resultant dissociation of intentional or spontaneous contralateral conjugate gaze in both eyes (Bender and Weinstein, 1944). The syndrome of a lesion within the median longitudinal fasciculus, first described in man with anatomical studies by Spiller (1924), consists of paralysis of adduction with preserved convergence of the ipsilateral eye and horizontal nystagmus in the contralateral abducting eye. The same pattern is found in the monkey. After an electrolytic lesion confined to the right bundle, electrical stimulation of the right frontal (arcuate) cortex induced contralateral gaze which was dissociated, and there was paralysis of adduction of the right eye and horizontal nystagmus in the abducting left eye. These findings suggest that a pathway, which subserves conjugate horizontal eye movement to the left, descends from the right cerebrum and crosses to the left pontine reticular formation and on to the left nu. abducens. From the left abducens nucleus this pathway recrosses the midline, and in its ascent to the right nu. oculomotorius can be blocked by a lesion in the right median longitudinal fasciculus with consequent paralysis of adduction in the right eye. It should be emphasized that the same lesion in the right median longitudinal bundle also results in a dysfunction of the left abducens nucleus with a phasic motor instability (nystagmus) in the left abducted eye. The pathophysiological basis for the nystagmus in the abducted eye is still unclear. This ocular instability in the abducting eye may be explained by the recent morphophysiological studies which demonstrated a reverse pathway within the median longitudinal fasciculus. Impulses from internuclear neurons of the nu. oculomotorius project caudally through the ipsilateral fasciculus and across to the contralateral nu. abducens (Maciewicz, Kaneko, Highstein and Baker, 1975; Büttner-Ennever, 1977, and personal communication). In summary, these electrophysiological and anatomical observations suggest that a lesion in this fasciculus causes (1) blocking of ascending impulses to the oculomotor nucleus with paralysis of adduction of the ipsilateral eye and (2) interference with descending impulses projecting to the contralateral abducens nucleus with resultant instability of abduction or nystagmus in the contralateral abducting eye. These bi-directional paths within the fasciculus are illustrated in the diagram in fig. 2. A lesion within the median longitudinal fasciculus did not abolish convergence in either eye.

(6) *Vertical Eye Movements Impaired by Lesions Within the Brain*

(a) *Unilateral lesions.* Lesion within the oculomotor pathway on one side of the brain, such as a hemidecortication, not only caused paralysis of horizontal gaze but produced subtle defects in vertical eye movements as well. These defects in vertical gaze appeared on bilateral vestibular stimulations. Thus, bilateral thermokinetic stimulations of the ear canals in a hemidecorticate monkey resulted in ipsilaterally oblique movements rather than the anticipated pure upward or downward deviations (Pasik *et al.*, 1960). Impairment of either downward or upward ocular movements was also found in lesions of deeper structures. The defect was elicited on bilateral vestibular stimulation and the direction of impairment, whether up or down, depended upon the location of the unilateral lesion. Following a unilateral (3 to 5 mm) lesion in the diencephalon, bilateral thermokinetic stimulations of the ear canals revealed defects in the expected

TABLE 4. VERTICAL OCULOMOTOR RESPONSES ON BILATERAL SIMULTANEOUS CALORIC STIMULATIONS OF BOTH EAR CANALS IN AN ALERT MONKEY WITH A 2 TO 4 MM ELECTROLYTIC LESION IN THE LEFT DIENCEPHALON

Caloric stimulus	*Ear stimulated*	*Direction of binocular movement*	
		Upward vector	*Downward vector*
Cold	Bilateral	Upward nystagmus preserved	Tonic deviation downward defective
Warm	Bilateral	Tonic deviation upward preserved	Downward nystagmus defective

downward (slow phase or saccadic) movements (Table 4), whereas following a small unilateral lesion in the pontine tegmentum, bilateral caloric stimulations resulted in an impairment of expected upward (slow phase and saccadic) eye movements (Table 5). Thus, downward binocular movements were altered by a unilateral lesion above the level of the oculomotor decussation, while upward binocular movements by a lesion below this level (Shanzer and Bender, 1959). In each instance, the defects in vertical eye movements caused by the unilateral lesion were elicited only with bilateral vestibular stimulations. These findings again indicated that unilateral oculomotor pathways contain the sources of both horizontal and vertical vectors and that the downward were more rostrally situated than the upward.

Unilateral lesions within the nu. oculomotorius revealed a topographical pattern similar to that observed in stimulation experiments. A lesion in the rostral pole of this nucleus resulted in an impairment of monocular downward movement, whereas a lesion in the caudal portion resulted in a defect in upward movement of the ipsilateral eye (Bender and Weinstein, 1943).

A small lesion within the right median longitudinal fasciculus not only disrupted contralateral horizontal gaze to the left but also impaired monocular movements in the vertical plane. In such a preparation electrical stimulation of the left posterior semicircular canal failed to induce downward movement of the right eye, as expected in the normal monkey. The latter suggested an interruption of a

TABLE 5. VERTICAL OCULOMOTOR RESPONSES ON BILATERAL SIMULTANEOUS CALORIC STIMULATIONS OF BOTH EAR CANALS IN AN ALERT MONKEY WITH 1 TO 2 MM ELECTROLYTIC LESION IN THE LEFT PARAMEDIAL ZONE OF TEGMENTUM OF PONS

Caloric stimulus	*Ear stimulated*	*Direction of binocular movement*	
		Upward vector	*Downward vector*
Cold	Bilateral	Upward nystagmus impaired	Tonic deviation downward preserved
Warm	Bilateral	Tonic deviation upward impaired	Downward nystagmus preserved

pathway which subserves monocular vertical movements. Evidently, impulses transmitted from the left vestibular nucleus were blocked by a lesion within the right fasciculus in their course to the right nu. oculomotorius (Shanzer, Goto, Cohen and Bender, 1964).

In bilateral lesions of the median longitudinal fasciculus there were bilateral horizontal ocular defects, namely, lack of motion in the adducting eye and nystagmus in the abducting eye with preserved convergence. In addition, there was now visible impairment of vertical gaze in both eyes. The latter was indicated by upbeating nystagmus on upward gaze and, in some, by downbeating nystagmus on downward gaze (Bender and Weinstein, 1950; Evinger, Fuchs and Baker, 1977). It seems that both horizontal and vertical eye movements are partly mediated through this fasciculus. The foregoing observations indicate that there are bi-directional pathways within one median longitudinal fasciculus which conduct (a) contralateral horizontal and (b) vertical (up and down) vectors. Evidently, this bundle does not transmit impulses for ocular convergence. The latter must be subserved by a different pathway.

(b) *Bilateral lesions of the cerebrum.* Whereas unilateral lesions within the cerebrum caused impairments in contralateral horizontal and subtle defects in vertical gaze, lesions on both sides of the brain revealed gross defects for eye movement, both in the horizontal and vertical planes.

Large bilateral lesions within the cerebrum or multiple small focal lesions, e.g., within the 'globus pallidus' and in the region of the internal capsule of man, have been known to produce impairment of ocular gaze in all directions, among other motor deficits. Bilateral lesions of the frontal cortex and the underlying white matter and putamen may result in loss of voluntary vertical eye movement or a complete loss of all voluntary eye movements in man (Tiling, 1873–4; Tournier, 1898).

Bilateral frontal lobectomies in the monkey and man caused a paucity of spontaneous eye movements (Smith, 1944). Bilateral removal of area 17 in the monkey did not abolish spontaneous eye movements, but larger lesion in the occipital lobe, including areas 17, 18 and 19, reduced the frequency of spontaneous eye movements (P. Pasik and T. Pasik, 1964). These monkeys did not exhibit the usual full visual responses, although after the first week they had good optokinetic but weak optokinetic after nystagmus.

(c) *Split-brain preparations and optokinetic nystagmus.* Defects in vertical optokinetic nystagmus were produced by split-brain preparations in which the two hemispheres were virtually disconnected. Following section of the optic chiasma and the corpus callosum, purely vertical nystagmus, which could be elicited on monocular stimulation in the normal monkey, resulted in oblique nystagmus. In this situation the unilateral vertical visual stimuli projected only into one of the two hemispheres. It was the lack of sensory input into both hemispheres which interfered with full expression or manifestations of the two vertical vectors, as would be expected when the right and left hemiretina of one eye were stimulated. The resultant oblique nystagmus was the vector sum of horizontal and one of the vertical components activated within one cerebral hemisphere. Thus, the horizontal component pulled the eyes obliquely to the side of the 'deprived' hemisphere (Pasik *et al.*, 1971). When both eyes of the split-brain preparation were simultaneously stimulated, the vertical vectors in both hemispheres were activated and the nystagmus was purely vertical.

(7) *Bilateral Lesions of Deeper Structures*

Bilateral lesions in deeper structures resulted in more specific impairments of eye movements in the vertical plane. Clinical examples of distinct paresis in the vertical plane, especially for downward gaze, were found among patients with bilateral disease of the basal ganglia, for example, in Parkinsonism (Corin, Mones, Elizan and Bender, 1972) and in more extensive bilateral involvement of the diencephalon and upper brain-stem, such as in patients with progressive supranuclear palsy (Steele, Richardson and Olszewski, 1964; David, Mackey and Smith, 1968; Steele, 1972). Cases of paralysis of both upward and downward gaze with preserved horizontal movement have been frequently observed in man (Spiller, 1905). Such patients had bilateral extensive lesions in the diencephalic and mesencephalic regions, pressing on structures above the level of the oculomotor nuclei. Other than gross localization of the pathology, there were few attempts for a more precise correlation of the implicated structure and the ocular dysfunction. Many believed that defects in vertical gaze were due to lesions within the superior colliculi but this theory could not be verified by experimental ablations of the tectum (Bernheimer, 1899; Ferrier and Turner, 1901; Pasik, Pasik and Bender, 1966). Paralysis of vertical gaze was also attributed to lesions of the accessory oculomotor nuclei. Carpenter (1971), however, could not confirm that defects in vertical gaze could be produced by lesions either of the interstitial nucleus of Cajal or of the nucleus of Darkschewitsch.

(a) *Paralysis of upward gaze.* The syndrome of paralysis of upward gaze has been frequently observed in tumours in the region of the pineal gland. Such lesions usually implicate so many structures within the mesodiencephalic region that it has been difficult to ascertain the precise site responsible for the syndrome. Collier (1927) described a patient with eyelid retraction and paralysis of vertical gaze. At autopsy this patient had a capsulo-thalamic hæmorrhage with destruction of the adjacent posterior commissure. However, there was no mention whether there was a relation between the paralysis of upward gaze and the lesion of the posterior commissure. In a clinicopathological study of 27 patients with paralysis of vertical gaze, Christoff (1974) found the critical areas commonly affected were both sides of the pretectum or unilateral pretectum and part of the posterior commissure. This deduction was based on experiments which reproduced the syndrome of paralysis of upward gaze in the monkey (Pasik, Pasik and Bender, 1969; Pasik and

Pasik, 1974). In the latter, investigators found that small (1 to 2 mm) bilateral electrolytic lesions within the pretectum or a single 'razor cut' section of the posterior commissure resulted in a paralysis of upward gaze, eyelid retraction, loss of convergence and impaired pupillary reflexes. In addition, 4 of the 10 monkeys showed transient and less prominent impairments of downward gaze. The alterations in upward eye movements were for spontaneous gaze, for those associated with eyelid closure and the saccades induced by optokinetic or bilateral vestibular stimulations, as summarized in Table 6. When the optokinetic stimuli were directed straight downward, there was no upward nystagmus. Instead of expected upward nystagmus there were binocular adduction saccadic movements or convergent nystagmus. When the optokinetic stimuli moved obliquely downward, there was horizontal instead of the oblique nystagmus, as one would expect in the normal. The foregoing oculomotor dysfunctions may be classified as the *syndrome of a lesion of the posterior commissure.*

TABLE 6. VERTICAL OCULOMOTOR RESPONSES ON BILATERAL SIMULTANEOUS CALORIC STIMULATIONS OF BOTH EAR CANALS IN AN ALERT MONKEY WITH ELECTROLYTIC LESION IN THE POSTERIOR COMMISSURE OR BILATERAL PRETECTAL LESIONS

Caloric stimulus	*Ear stimulated*	*Direction of binocular movement*	
		Upward vector	*Downward vector*
Cold	Bilateral	Upward nystagmus lost	Downward tonic deviation preserved
Warm	Bilateral	Upward tonic deviation lost	Downward nystagmus preserved

(b) *Paralysis of downward gaze.* Descriptions of lesions causing the syndrome of paralysis of downward gaze with preserved upward and horizontal gaze were reported in man by Schuster (1921), André-Thomas, Schaeffer and Bertrand (1933), Jacobs, Anderson and Bender (1973), Cogan (1974) and Halmagyi, Evans and Holliman (1978). In our case described by Jacobs *et al.* (1973) autopsy disclosed bilateral large vascular lesions localized to the median thalamus and bilateral destructions in the region of the fasciculus retroflexus, the habenular nuclei, as well as the rostromedial portions of the red nuclei and adjacent structures. The region of the posterior commissure, pretectal and more caudal levels were relatively preserved. This patient showed no slow or quick phase movements in a downward direction on bilateral thermokinetic or optokinetic stimulations. Optokinetic stimulations directed obliquely upward yielded only horizontal nystagmus instead of obliquely downward nystagmus. The downward vector was absent and only the horizontal was active. Denny-Brown and Fischer (1976) and Denny-Brown (1977) reported that bilateral lesions within the diencephalon, extending from the level of the median thalamus to that of the posterior commissure, caused paralysis of both upward and downward gaze in the monkey. Their lesion may have extended ventrally across the hypothetical transverse plane.

The foregoing clinicopathological and experimental studies suggested that the lesion responsible for paralysis of downward gaze was situated more rostrally than the posterior commissure site where a lesion caused paralysis of upward gaze (Pasik *et al.*, 1969). Therefore, after numerous trials of bilateral electrical stimulation and lesion experiments in the monkey, Kömpf, Pasik and Pasik (1977) and Kömpf *et al.* (1979) made small electrolytic lesions (1 to 1.5 mm in diameter) localized to the rostral and medial borders of the two red nuclei, about 1 mm from the midline and medial to the fasciculus retroflexus. This fasciculus was not involved. The two lesions appeared to implicate the rostral interstitial nucleus of the median longitudinal fasciculus, described in detail by Büttner-Ennever and Büttner (1978). These bilateral lesions resulted in an isolated paralysis of downward gaze. The paralysis of downward and preserved upward and horizontal movements lasted many weeks. No downward tracking or saccadic movements could be induced by bilateral vestibular or by optokinetic vertical stimulations in these monkeys (Table 7). Optokinetic stimuli moving obliquely upward resulted in horizontal nystagmus instead of the expected obliquely downward saccades, that is, the vertical vector was absent. In some of the monkeys there were also defects in upward gaze, indicating that there is no sharp demarcation between upward and downward direction and may explain why so many clinical and experimental syndromes include defects in both directions. Unilateral lesions in the region of the *rostral* interstitial nucleus of the median longitudinal fasciculus did not result in paralysis of downward gaze.

From the foregoing observations it is evident that paralysis of downward gaze occurs specifically after discrete bilateral lesions within the diencephalo-mesencephalic junction, and paralysis for upward gaze in slightly more caudally situated lesions, precisely in the posterior commissure or both sides of the pretectum. At this junction there is a hypothetical transverse plane which narrowly separates the zone concerned with downward gaze from the more caudal area

TABLE 7. VERTICAL OCULOMOTOR RESPONSES ON BILATERAL SIMULTANEOUS CALORIC STIMULATIONS OF BOTH EAR CANALS IN AN ALERT MONKEY WITH BILATERAL 2 MM ELECTROLYTIC LESIONS IN THE DIENCEPHALON NEAR THE MIDLINE AT THE LEVEL OF THE ROSTRAL INTERSTITIAL NUCLEUS OF THE MEDIAL LONGITUDINAL FASCICULUS

Caloric stimulus	*Ear stimulated*	*Direction of binocular movement*	
		Upward vector	*Downward vector*
Cold	Bilateral	Upward nystagmus good	Tonic deviation severely impaired. Lost below horizontal plane
Warm	Bilateral	Excellent upward tonic deviation	Downward nystagmus absent

which is involved in upward gaze. Therefore, it is not surprising that a pathological or experimental lesion at this mesodiencephalic level or transverse plane may result in defects in both upward and downward directions. It should be emphasized that defects in vertical gaze *were not* due to implication of the accessory oculomotor nuclei (Carpenter, Harbison and Peter, 1970; Hassler, 1972).

(c) *Defects in vertical gaze due to lesion in the pons.* Whereas clinical and experimental studies indicate that paralysis of upward eye movements is caused by lesions at the pretectal-posterior commissure levels and paralysis for downward gaze more rostrally at the red nucleus-thalamic level, there are instances in which pontine lesions also produce impairments of vertical eye movements, e.g. nystagmus on upward or on downward gaze. Bilateral lesions of the median longitudinal fasciculus in the pontine tegmentum, located just caudal to the trochlear nuclei, resulted in downbeating nystagmus on downward gaze, while those situated more caudally near the level of the abducens nuclei resulted in upbeating nystagmus on upward gaze (Bender and Shanzer, 1964; Evinger *et al.*, 1977). Furthermore, midline section between the right and left fasciculi, caudal to the level of the abducens nuclei, extending through the medullary tegmentum resulted in a downbeating nystagmus. The foregoing observations indicate that the pathways which transmit eye movements in the vertical plane, namely, for downward gaze, can be detected even in most caudal regions of the brain-stem, for example, at the level of the medulla. Bilateral lesions in the pontine reticular formation caused paralysis of right and left horizontal eye movements with preserved vertical gaze. However, if in addition to those bilateral pontine lesions the median raphe was sectioned in the monkey, there resulted paralysis of conjugate gaze in all directions, horizontal, oblique and vertical planes, without affecting the pupillary or eyelid motions (Bender and Shanzer, 1964). Similar findings were observed in man by Hoyt and Daroff (1971) and Christoff (1974).

(d) *Lesions of the semicircular canals and vestibular nuclei.* It has been known for years that the vestibular system influences eye movements (Flourens, 1842). Unilateral destruction of the semicircular canals results in an instability of conjugate gaze with a jerking nystagmus to one side. Bilateral destruction of the semicircular canals results in a loss of optokinetic after-nystagmus in the monkey (Uemura and Cohen, 1975) and inability to maintain fixation of a stationary target during head or body movement in man (Ford and Walsh, 1936; Bender and Feldman, 1967). Unilateral electrolytic lesion within the vestibular nucleus in the monkey usually causes instability of contralateral ocular gaze with nystagmus (Cohen, 1974). Bilateral lesions of the vestibular nuclei in man cause a loss of the vestibulo-ocular reflex. There is instability of ocular fixation during head-body motion. In none of these lesions is there a paralysis of conjugate gaze in any one direction. There is only an instability of maintaining ocular gaze in the horizontal and vertical planes.

All the foregoing stimulation and lesion data confirm the theory that the motor pathways which transmit impulses for eye movements in the vertical plane are bilaterally activated by sensory (vestibular or visual) inputs. The oculomotor pathways transmitting horizontal and vertical impulses within the cerebrum are bilateral and project down through the mesodiencephalon where the right and left sides decussate and continue to the ponto-medullary reticular formation. The downward and upward vectors tend to maintain a rostro-caudal relationship through the mesodiencephalic region, near the midline, down to the oculomotor nucleus. Below this level the pathways for vertical (up and down) eye movements rearrange themselves but the exact topography is as yet unknown. It is possible that the oculomotor pathways subserving both horizontal and vertical eye movements within the brainstem may be concentrated in the midline of the pontine tegmentum; those for vertical being more medial, while those for horizontal being slightly lateral to the midline.

In summary, we may infer from the evidence provided by stimulation and lesion studies in the monkey and man that brain control of conjugate eye movements is subserved by bilateral pathways which project into the brain-stem. At the level of the diencephalon these pathways follow a generally paramedian course through the subthalamic and mesodiencephalic regions into the reticular formation. Pathways representing horizontal gaze undergo an electroanatomically verified decussation across the midsagittal plane at the level of the oculomotor trochlear nuclei. It is probable that vertical binocular movements are also mediated by the same pathways which transmit horizontal gaze so that both the horizontal and vertical vectors decussate across the midsagittal plane at the same level. However, there is doubt whether there is a crossing of pathways mediating upward and downward binocular movements across a transverse plane. The vertical components appear to be transmitted by pathways that maintain their side of origin, either right or left. The downward vectors are predominant within the median diencephalon, while the upward vectors are situated more ventrally in the oral mesencephalon, i.e. the pretectum and posterior commissure. More caudally at the level of the nu. oculomotorius the same pattern of response for vertical monocular movements was found. The vectors for monocular downward movement were operative at the rostral pole, while those for upward were in the caudal region of the oculomotor nucleus.

The efferent pathways transmitting vertical eye movements can be identified by bilateral simultaneous electric stimulations of the brain, by bilateral stimulations of afferents within the vestibular or visual systems, by making bilateral lesions or by a combination of two methods. However, the morphology of these corticofugal pathways has not been fully identified by the usual axonal or modern tracer techniques. The structural as well as the 'electroanatomical' connections between the cerebrum and lower levels still remain unknown. More modern electrophysiological techniques, e.g. recording of electrical activity within the above defined pathways during eye movements has further advanced our knowledge of the oculomotor system.

ELECTROPHYSIOLOGICAL STUDIES WITHIN THE BRAIN

Recording of electrical activity within the pontine tegmentum before and during eye movements was first reported by Duensing and Schaefer (1957). Since then numerous extra- and intracellular studies were conducted in various regions of the brain, including the occipital lobe, thalamus, lateral geniculate body (Shanzer, Wagman and Bender, 1962; Cohen and Feldman, 1968; Feldman and Cohen, 1968) and other parts of the cerebrum (Bizzi, 1968; Bizzi and Schiller, 1970; Robinson, 1970; Mountcastle, Lynch, Georgopoulos, Sakata and Aeuna, 1975; Mountcastle, 1977). The locations of foci which yield electrical activity during conjugate eye movement appeared to be just as widespread as those which on electrical stimulations produced conjugate deviations. Moreover, such recordings during eye movements were complicated by the presence of visual receptor cells within different regions of the cerebral cortex. Connections between the various regions of the cerebral cortex and the cells in the thalamus, basal ganglia, superior colliculi, cerebellum and brain-stem have been but sparsely demonstrated. For technical reasons the recordings were usually from one focus within a particular zone. Simultaneous samplings from one or both sides of the cerebrum or brain-stem were seldom recorded because the studies were fraught with too many uncontrolled variables. Most of the studies dealt with excitatory rather than inhibitory activities.

During the past twenty years there appeared a plethora of reports of studies of electrical activity within the brain-stem during saccades and less during slow phase movements (Raphan and Cohen, 1978). Attempts were made to identify brain-stem oculomotor pathways which transmit impulses for eye movements in the horizontal, oblique, or vertical planes but results are still inconclusive. These investigations relied upon two main approaches: (1) extracellular recordings from tissues before and during eye movements saccades in alert monkeys; (2) intracellular recordings in anæsthetized cats to map direct pathways between various neurons mostly in the reticular formation of the pons and mesencephalon, vestibular and ocular nuclei (Sasaki, 1963; Cohen, 1975).

Recordings from Brain-stem Structures

(1) *Reticular formation (pontine and mesencephalic).* During the past few years electrophysiological and newer anatomical investigations revealed disynaptic projections from the reticular formation to the ocular nuclei (Highstein, Cohen and Matsunami, 1974) but there was little physiological evidence for the existence of direct pathways from this region to all eye muscle motoneurons. Internuclear neurons within the abducens nucleus which were first demonstrated morphologically by Fuse (1912) can now be identified electrophysiologically to interconnect various cell masses. Cells within the pontine reticular formation on one side which receive impulses from the right and left vestibular nuclei and from the prepositus nucleus project axons to the abducens nucleus. Unit activity within the

paramedian pontine reticular formation was obtained during ipsilateral eye movements. Activity was also recorded in the paramedian zone during contralaterally directed horizontal or oblique binocular movements but the activity was more conspicuous during ipsilateral binocular movements. Single unit recordings also showed that the neurons within the pontine reticular formation encode parameters of both horizontal and vertical fast eye movements (Luschei and Fuchs, 1972; Henn and Cohen, 1976). The pontine reticular formation has been considered as a functional unit and contains bilaterally symmetrical supranuclear units that collaborate to produce co-ordinate conjugate movements in the horizontal and to influence vertical gaze as well (Büttner-Ennever, 1979).

To date studies within the mesencephalic reticular formation have been few. Most of the unit activity was obtained during oblique or vertically directed eye movements (King and Fuchs, 1977). Unit activity during oblique movement was more prominent when there was a contralateral component.

(2) *Nucleus prepositus hypoglossi* (*nu. prepositus*). The cells of this nucleus, which were first recognized anatomically by Marburg (1931), lie dorsally to those of the hypoglossal nucleus and extend beneath the floor of the 4th ventricle to the level of the abducens nucleus. Recently it was discovered that these cells participate in eye movements (Baker and Berthoz, 1975). Electrical stimulation of the prepositus nucleus results in ipsilateral conjugate horizontal eye movements. It has been postulated that the nu. prepositus has the requisite connections for combining information from the pontine reticular substance and ocular nuclei with the afferents from the vestibular and visual systems, as well as afferents from the cervical muscles, so as to generate eye movements (Baker, 1977*a*). Further evidence that the nu. prepositus is connected with the vestibular and visual system is that unilateral lesions of the prepositus at the level of the abducens nucleus in the monkey can cause impairment of oculomotor function in the form of a bilateral loss of optokinetic after-nystagmus in the horizontal, vertical or oblique planes (Uemera and Cohen, 1975).

(3) *Oculomotor nucleus* (*nu. oculomotorius*). Electrophysiological investigations of nu. oculomotorius have been conducted mostly in relation to studies of the nu. abducens, particularly as to the activity of the motoneurons innervating the medial rectus during horizontal conjugate gaze (Highstein, Maekawa, Steinacker and Cohen, 1976). Many of the recently discovered projections to the nu. oculomotorius ascend from the nuclear masses within the pons and medulla, contralateral abducens and ipsilateral nu. prepositus. Also there are internuclear connections between the oculomotor-trochlear nuclei and the vestibular nuclei. Neurons relaying excitation from the anterior canal through the median longitudinal fasciculus or through the brachium conjunctivum to nu. oculomotorius have also been found (Highstein, 1973, 1974; Baker and Highstein, 1978; Yamamoto, Shimoyama and Highstein, 1978). These findings confirmed the monocular vertical movements obtained on electrical stimulation of the anterior

canal and the paralysis of such movement after lesion of the median longitudinal fasciculus (Shanzer *et al.*, 1964). There have been few unit cell recordings within the nu. oculomotorius during conjugate vertical gaze. Descending projections from the *rostral* interstitial nucleus of the median longitudinal fasciculus involving vertical gaze were demonstrated by Büttner-Ennever and Büttner (1978). Massive projections from the tegmentum to the nu. oculomotorius or internuclear neurons connecting the right and left oculomotor nuclei could not be established. Projections descending from the oculomotor nucleus to both abducens nuclei have been demonstrated by Maciewicz *et al.* (1975).

(4) *Abducens nucleus* (*nu. abducens*). The abducens nucleus contains all the cells necessary for ipsilateral conjugate gaze. Besides the large motoneurons which innervate the external rectus muscle, there are many different sets of non-motoneurons (Baker and McCrea, 1979). Most of these non-motoneurons are the internuclear neurons which send axons across the midline to the opposite median longitudinal fasciculus and ultimately to the motoneurons within the nu. oculomotorius that innervate the medial rectus muscle. The first electrophysiological experiments which differentiated motoneurons from other neurons within the abducens nucleus were those of Baker and Highstein (1975). This nucleus receives projections mostly from the ipsilateral pontine reticular formation (Büttner-Ennever and Henn, 1976), transmitting both excitatory and inhibitory impulses (Highstein and Baker, 1978). The abducens also receives axons from both vestibular nuclei, the ipsilateral nucleus prepositus and the dorsomedial medullary reticular formation (Baker, 1977*b*). The contralateral vestibular nucleus has an excitatory while the ipsilateral has an inhibitory effect on the motor and internuclear neurons within the nu. abducens (Maciewicz, Egan, Kaneko and Highstein, 1977). As mentioned above, morphophysiological studies have suggested that internuclear neurons within or around the nu. oculomotorius project downward to the abducens nuclei of the cat (Maciewicz *et al.*, 1975).

(5) *Median longitudinal fasciculus.* It has been generally accepted that the median longitudinal fasciculus is an important anatomical pathway for the vestibulo-ocular reflex. Previous anatomical studies have shown that this bundle is bidirectional. It contains mostly ascending fibres but past anatomical studies have also demonstrated the existence of descending axons (Lorente de Nó, 1933; Pompeiano and Walberg, 1957; Carpenter, 1971).

Traditionally, activity within the median longitudinal fasciculus has been thought to be directly under vestibular influence but recent experiments have demonstrated that this bundle contains axons of internuclear neurons, originating within the contralateral abducens nucleus and in the ipsilateral n. prepositus (Highstein, 1977*a*; Maciewicz *et al.*, 1977). Of these, the internuclear neurons arising from the contralateral abducens nucleus are the major source of fibres within the bundle. These neurons are involved in the transmission of horizontal gaze (Baker and Highstein, 1975; Delgado-Garcia, Baker and Highstein, 1977).

Other experiments indicate that the fasciculus also transmits impulses for vertical eye movements (Evinger *et al.*, 1977). Pola and Robinson (1978) found that the firing within this bundle increased during an upward or downward eye position. These fibres for vertical (up and down) eye movements were located in the central portion of the fasciculus but no separation between up and down activity could be demonstrated.

(6) *Other structures which influence conjugate eye movements.* The electrophysiology of the vestibular and other systems which influence eye movement is too complex a subject to discuss in this communication.

(a) As noted from the stimulation and lesion studies (Cohen, 1971, 1974; Uemera and Cohen, 1976) the vestibular nuclei play an important role in regulation of the vestibulo-ocular reflex. Intracellular studies of the vestibulo-ocular reflex have been summarized by Wilson and Melvill Jones (1979).

(b) Electrophysiological investigations of the cerebellum have disclosed that the flocculus is an important site for visual and vestibular interactions both of which affect ocular movement (Ito, 1972, 1977; Ito, Nisimara and Yamamoto, 1973; Miles, 1977). Since the cerebellum receives projections from vestibular and neck muscle afferents, as well as from the accessory optic system, it is probable that oculomotor function can be altered by activation of any one or a combination of these afferents.

(c) The superior colliculus is a complex structure with multiple inputs and outputs but despite the various morphophysiological investigations there is doubt whether the colliculus plays an important role in conjugate eye movements. Traditionally, the colliculus has been considered as a 'centre' for reflexive movements of the eyes in response to visual stimuli but stimulation and lesion studies conducted during the past eighty years have not been conclusive.

The colliculus probably facilitates visuo-oculomotor processes but it neither locates visual targets nor programmes eye movements. A review of the recent numerous electrophysiological investigations indicates that the only clear function of this structure is concerned with the initiation of saccadic eye movement (Sparks and Pollack, 1977). The accuracy and velocity of saccades are unaffected by tectal lesions (Wurtz and Goldberg, 1972). The collicular influences on motoneurons of the extraocular muscles is probably through polysynaptic connections and disynaptic pathways.

After a review of some of the massive electrophysiological data obtained from experiments in the various subcortical structures listed above, an attempt was made to interpret this information in terms of direction of saccadic or tracking binocular movement, i.e., horizontal and vertical vectors activity.

(7) *Summary of electrophysiology of direction of eye movements.* (a) Horizontal eye movements. Units in the motor nuclei fire at constant rates in association with eye position and bursts in association with saccades (Cohen and Henn, 1972; Henn

and Cohen, 1972). It has long been known that the paramedian pontine reticular formation is involved in ipsilateral conjugate gaze. Bursts of activity and a steady level of activity of motoneurons appear to originate from the pontine reticular formation and periabducens region, where cells associated with ipsilateral horizontal eye movement have been identified (Henn and Cohen, 1976; Keller, 1974). Activity of many cell units situated within the pontine reticular formation and around the nu. abducens were correlated with all types of eye movements (Fuchs and Luschei, 1970; Luschei and Fuchs, 1972) but predominately with ipsilaterally directed saccades. Moreover, electrical stimulation through the microelectrodes at these points resulted in ipsilateral conjugate eye movements, confirming the previous electroanatomical studies.

Projections to the nu. abducens reach two classes of cells within the abducens complex (i) the motoneurons innervating the external rectus muscle and (ii) a group of cells which are not motor neurons, and best designated as internuclear neurons (Baker and Highstein, 1975; Highstein, 1977*b*). The internuclear neurons cross the midline and enter the opposite median longitudinal fasciculus to ascend towards the motoneurons of the medial rectus muscle. Thus, on stimulation of the paramedian pontine reticular formation there is simultaneous activation of (a) the motoneurons of the abducens nucleus resulting in ipsilateral abduction and (b) of the internuclear neurons which induce contralateral adduction, together yielding ipsilateral horizontal conjugate eye movement. This physiological organization for horizontal gaze has been confirmed morphologically by orthograde transport of labelled amino acids from the nucleus reticulopontis caudalis and oralis (Büttner-Ennever and Henn, 1976; Graybiel, 1977*b*). Thus, modern electrophysiological investigations support the theories for mechanism of ipsilateral horizontal gaze first proposed by various clinicians in the nineteenth century (A. Foville, 1858; Wernicke, 1877). There is still no electrophysiological information as to the prepontine pathway or the corticofugal projection which theoretically decussates in the midbrain and connects with the reticular formation.

(b) Vertical eye movements. The mesencephalic reticular formation has many cells which are associated with vertical eye movements. One site of supranuclear mediation of *vertical gaze* was found in a portion of the reticular formation at the mesodiencephalic junction where unit activity was associated with vertical saccades (Büttner, Büttner-Ennever and Henn, 1977). This region, especially the rostral interstitial nucleus of the median longitudinal fasciculus, receives ascending projections from the pontine reticular formation (Büttner-Ennever and Büttner, 1978). Anatomically these ascending fibres which lie lateral to the median longitudinal fasciculus degenerate after lesions in the pontine reticular formation (Goebel *et al.*, 1971). In both the mesencephalic and pontine reticular formations there were no units which could be recorded in association with purely vertical movements. Only movements which were oblique or 'off vertical', i.e. 5 to 15 deg from the vertical plane could be detected. These electrophysiological findings support the theory that to attain purely vertical eye movement, the horizontal vectors (to right and left) must be neutralized, for example, by bilateral simultaneous stimulations.

Although parts of the neural mechanism for vertical and horizontal gaze are separate, there is fragmentary evidence to suggest that all types of saccades may be activated from the region of the pontine reticular formation. The median longitudinal fasciculus shows 'tonic burst' activity during horizontal saccades and signals of tonic vestibular pauses in association with vertical (up or down) eye movements (Pola and Robinson, 1978). From anatomical studies Carpenter (1971) and Tarlov (1972) indicated that fibres from the median longitudinal fasciculus 'contact' the motoneurons of vertical eye muscles.

In extracellular recording studies of the median longitudinal fasciculus near the trochlear nucleus, King, Lisberger and Fuchs (1976) and King and Fuchs (1977) found that there were two functional classes of fibres, namely, those which transmitted impulses to the medial rectus neurons for horizontal conjugate eye movement induced by vestibular or visual stimuli and those which transmitted impulses for vertical gaze. These results provide more evidence for anatomical and functional separation of horizontal from vertical eye movement mechanisms in the pons and mesencephalon.

All available evidence derived from unit cell studies suggests that the pontine reticular formation contains the main neural substrate for originating and co-ordinating conjugate eye movement in all directions. This is the same area in which bilateral lesions, extending across the midline, caused paralysis of conjugate gaze in all directions in the monkey and man (Bender and Shanzer, 1964; Hoyt and Daroff, 1971; Christoff, 1974). Bilateral lesions in the median longitudinal fasciculi also affected horizontal and vertical gazes (Bender and Weinstein, 1943; Evinger *et al.*, 1977).

In general, numerous relays have been found between various nuclear masses, extending from the levels of the diencephalon to that of the medulla, ipsilaterally and contralaterally (Raphan and Cohen, 1978), but none of these investigations revealed a clear-cut organization of pathways above the level of the diencephalon. It appears that integration of oculomotor drives probably occurs centrally and in polysynaptic networks encompassing the three ocular nuclei, as well as those of the pontine reticular formation, the nu. prepositus and the vestibular nuclei.

In summary, some progress has been made in identifying the direction of flow of impulses between some of the nuclear masses within the brain-stem which participate in conjugate eye movement. The decussation of pathways mediating vectors for various oculoversions may be found in the central portions of the mesencephalic and pontine reticular core. Vertical movements are usually mediated by pathways indistinguishable from those for horizontal movements but they are most readily identified in the mesencephalon. Whereas stimulation and lesion studies indicate different structures subserving up and down eye movements, electrophysiological recordings have not as yet revealed disparate extra- or intracellular unit activities, either preceding or during the two types of vertical ocular motions. In particular, no anatomical separation was found between upward and downward eye movements related to burst or tonic units (Büttner, Büttner-Ennever and Henn, 1977).

NEWER ANATOMICAL INVESTIGATIONS OF OCULOMOTOR PATHWAYS

There has been little advance in information about myelin sheath or axonal degenerations of corticofugal or brain-stem pathways (Kuypers and Lawrence, 1967). Anatomical connections between the cranial ocular nuclei and the pontine tegmentum and with the vestibular nuclei were reported but the findings were never conclusive (Lorente de Nó, 1933; Scheibel and Scheibel, 1958; Szentágothai, 1964). Recent developments emerging from retrograde tracing with horseradish peroxidase and orthograde tracings with radioactive amino acids have contributed much to the identification of some of the pre-oculomotor connections of the brain-stem structures with the 3rd, 4th and 6th cranial nerve nuclei (Lasek, Joseph and Whitlock, 1968; Graybiel and Devor, 1974). Several electrophysiological investigations cited above also employed axon-tracer techniques which in many instances confirmed the findings of single unit recordings. Autoradiographic investigations with injections of amino acids (3^H proline or 3^H leucine) into the pontine reticular formation have demonstrated connections between various nuclear masses, such as the nu. prepositus and the *rostral* interstitial nucleus of the median longitudinal fasciculus involved in the generation of conjugate eye movements. Mapping the pontine reticular formation by the anatomical tracer technique (Graybiel, 1977*a*) closely corresponds to mappings of this region derived previously from stimulation and lesion methods of Bender and Shanzer (1964) and Goebel *et al.* (1971), and from the more recent electrophysiological investigations of the brain-stem summarized by Raphan and Cohen (1978).

From the tegmentum of the pons autoradiographic tracer studies revealed: (a) a pathway from the caudal pontine reticular formation which projected to the ipsilateral abducens nucleus; (b) a descending projection to the ipsilateral adjoining nu. prepositus; (c) a decussating fibre system at the level of the abducens nuclei; and (d) an ascending group of fibres which extend ipsilaterally upward to the level of the 4th nerve nucleus (Graybiel, 1977*a*). Autoradiographic investigations in other laboratories confirmed and extended Graybiel's findings of projections from the pontine reticular formation to the ipsilateral abducens nucleus and from there to the contralateral median longitudinal fasciculus, and then on to the motoneurons of the nu. oculomotorius that innervate the contralateral internal rectus muscle (Büttner-Ennever, 1977; Büttner-Ennever and Henn, 1976). It must be emphasized that no fibres emanating from the pontine reticular formation make direct contact with the motoneuron somas of the contralateral internal rectus (Büttner-Ennever, 1977).

(1) *Horizontal Movements*

A morphological study employing the retrograde technique with horseradish peroxidase injected into the oculomotor nucleus indicates, as previously noted, that there are neurons within the abducens which are *not* motoneurons and which project (presumably *via* the median longitudinal fasciculus) to the contralateral motor neurons within the nu. oculomotorius innervating the medial rectus (Graybiel and Hartweig, 1974; Graybiel, 1977*b*). This important anatomical discovery was confirmed by Büttner-Ennever and Henn (1976) by the double labelling retrograde experiments of Steiger and Büttner-Ennever (1978) and by the extracellular unit cell recordings by Baker and Highstein (1975), Baker (1977*b*) and Highstein (1977*a*, *b*). These connecting neurons are now known as 'internuclear neurons' within the abducens nucleus. These internuclear neurons, first recognized anatomically by Fuse (1912) and now considered as part of the pre-ocular pathway for horizontal gaze, have also been identified with the electron microscope combined with tracer technique (Spencer and Sterling, 1977). Specifically, the axons of the internuclear neurons cross the midline at the level of the nu. abducens and ascend in the dorsal medial part of the contralateral medial longitudinal fasciculus, terminating on the motoneurons of the medial rectus (fig. 2). Previous anatomical investigations revealed that axons from the cells of the caudal pontine reticular formation projected directly to the nu. oculomotorius (Lorente de Nó, 1933; Scheibel and Scheibel, 1958; Szentágothai, 1964). Most recent electrophysiological studies have not supported these findings, although Highstein, Cohen and Matsunami (1974) found that axons from the paramedian pontine reticular formation transmit both excitatory and inhibitory impulses to the oculomotor nucleus. Studies of vestibulo-ocular connections showed prenuclear projections to agonist-antagonist motoneurons involved in horizontal eye movements (Maciewicz *et al.*, 1977; Baker and Highstein, 1978). Despite the considerable volume of simplifying data provided by the foregoing investigations, one should not assume the intrinsic neuronal organization for horizontal gaze to be completely defined. There are other mechanisms, such as torsional and vergence movements to be considered (Keller and Robinson, 1972). Impulses for vergent movements are conveyed by a separate supranuclear input to the motoneurons of the medial rectus (Delgado-Garcia *et al.*, 1977). This may explain why a lesion of the median longitudinal fasciculus impairs adduction but not vergent movements of the eye. The reason for the instability of the abducting eye, that is, nystagmus, in the syndrome of lesion within this bundle, as previously mentioned, may be found in the recent morphophysiological discovery of a downward projection of internuclear neurons from the nu. oculomotorius, extending caudally along the median longitudinal fasciculus to the opposite nu. abducens (Maciewicz *et al.*, 1975; Büttner *et al.*, 1975) (fig. 2).

(2) *Vertical Movements*

An ascending pathway concerned with vertical vectors was found to extend rostrally from the pons to the mesencephalon around the border of the oculomotor nucleus (Büttner, Hepp and Henn, 1977). Antegrade and retrograde tracer techniques have been used to label fibre connections to and from the mesencephalic tegmentum (Büttner-Ennever and Büttner, 1978). Unit cell recording in this region shows it to be a pre-oculomotor area for vertical eye movements but not specifically as to upward or downward (Büttner, Hepp and Henn, 1977). A cytologically distinct group of cells was culled in the diencephalomesoencephalic region by Büttner-Ennever and Büttner (1978). This cell group, previously described by Krieg (1948) and now referred to as *rostral* interstitial nucleus of the median longitudinal fasciculus, is located rostrally to the tractus retroflexus and to the interstitial nucleus of Cajal and ventrally to the nu. Darkschewitsch. By using radioactive anterograde tracer substances this rostral nucleus was found to receive inputs from cells of the pontine reticular formation and from the vestibular nuclei through compact pathways which ascend ventrally to the median longitudinal fasciculus (Büttner-Ennever and Henn, 1976; Büttner-Ennever and Büttner, 1978). Cells in this nucleus also send efferents to the oculomotor nuclei (Büttner-Ennever, 1979). With retrograde tracer technique a direct, predominately an ipsilateral, pathway was demonstrated to connect between the *rostral* interstitial nucleus of the median longitudinal fasciculus and the nu. oculomotorius (Büttner-Ennever and Büttner, 1978). Physiologically the cells in the *rostral* interstitial nucleus are involved in vertical binocular movements and interestingly, the right and left nuclei are interconnected *via* a commissure (Büttner-Ennever, 1979). It is in this area that bilateral electrical stimulations induce downward movements, while small bilateral electrolytic lesions cause paralysis of downward gaze (Kömpf *et al.*, 1977; Kömpf *et al.*, 1979). The latter results could not be reproduced by lesions in the nuclei of Darkschewitsch and Cajal, as previously believed.

Graybiel (1977*b*) also found direct projections from the subthalamic-prerubral regions to the ipsilateral oculomotor nucleus which correspond to the *rostral* interstitial nucleus of the median longitudinal fasciculus pathway. This prerubro-oculomotor connection may be part of an indirect path of an extrapyramidal input to the oculomotor complex. It is also probable that this pathway subserves downward eye movements, as derived from stimulation and lesion experiments (Spiegel *et al.*, 1964; Nashold and Gills, 1967; Denny-Brown and Fischer, 1976; Kömpf *et al.*, 1979).

(3) *Decussation*

Extensive studies using autoradiographic techniques suggested a high degree of differentiation in the supranuclear connections of the brain-stem oculomotor mechanisms, but there was no evidence of discrete 'crossings' of the oculomotor pathways in any one location. From the available electrophysiological data, reinforced by recent anatomical information, neurons within the pontine tegmentum could contribute fibres to the decussation in question. It may be that there is no single anatomical decussation but rather a number of crossings at different levels connecting the multiple nuclear masses mostly within the pontine brainstem, as proposed by M. Foville (1844) and Gubler (1856). Foville's concept of the decussation was that of a series of crossings within the centre of the brain-stem extended from the quadrigeminal plate to the pyramids in the medulla. Components of this core cross with their fellows of the opposite side along the entire length of the brain-stem and continue the crossing pattern down into the spinal cord.

According to Graybiel (1977*a*), there are many anatomical pathways which are part of a major system of decussating fibres connecting the two abducens nuclei (which in turn contribute to the right and left median longitudinal fasciculi, the two perihypoglossal nuclear masses, as well as the right and left vestibular nuclei). Some of the crossings between the oculomotor and abducens nuclei are at different levels and the anatomical pathways as elicited by tracing techniques extend mainly along the ventral and lateral edges of the median longitudinal fasciculus (Maciewicz *et al.*, 1975). Direct tegmento-ocular connections were difficult to demonstrate, although fibres from the nu. prepositus were shown to project directly to the ipsilateral oculomotor nucleus (Graybiel and Hartweig, 1974).

The finding that the nucleus pontis oralis and caudalis in the pontine tegmentum project ipsilaterally to the abducens nucleus, suggests that part of the decussation of oculomotor pathways across the midsagittal plane subserving horizontal movements may be found in the supranuclear or afferent fibres *en route* to the paramedial nuclei. The supposition is supported by autoradiographic studies at the level of the mesencephalic junction. Edwards (1975) found that descending fibres project downward from the nucleus cuneiformis, across the brachium conjunctivum, to terminate in the contralateral paramedian nuclei. Detailed discussion as to anatomical basis for an oculo- and cephalomotor crossing may be found in Graybiel's exhaustive review of this subject (Graybiel, 1977*a*). A number of more rostral tegmental fibre systems cross the midline at the level of the oculomotor and trochlear nuclei, including the dorsal and ventral tegmental decussations of Meynert and Forel and probably the posterior commissure, as well as the habenular commissure. It is possible that the posterior commissure is a bundle of decussating fibres which transmit impulses for upward movements, while the mainly ipsilateral axons emerging from the *rostral* interstitial nucleus of the median longitudinal fasciculus (Büttner-Ennever and Lang, 1978) near the fasciculus retroflexus may transmit impulses controlling binocular downward movements.

It is helpful to view the electroanatomical oculomotor decussation as fundamentally analogous to the crossing of pathways in the visual system. In each instance, there is a decussation of the system signalling or controlling activity in the right and left hemifields. In both the visual and oculomotor systems the decussation involves the crossing of the midsagittal plane, but in neither system is there a crossing of structures which subserve vertical activity between the superior and inferior half fields. In vision the anatomical crossing between the right and left nasal hemiretinæ in the primate is at the optic chiasm. In eye movement the corresponding decussation across the midsagittal plane is at the level of the midbrain. There is no anatomical or functional decussation across a transverse plane between the superior and inferior halves of the retinal projections (Polyak, 1957). Neither is there a crossing between the dorsal and ventral pathways which are involved in control of vertical eye movements across the horizontal meridian.

Based on clinical, pathological, experimental, physiological and recent anatomical studies it appears, as Graybiel (1977*a*) commented, that the oculomotor system is one of the most diffusely represented subsystems in the cerebrum and brain-stem and that its intrinsic organization is one of the most complex of any in the central nervous system.

SUMMARY

(1) It appears that all oculomotor pathways originating within the cerebrum and mediating horizontal, vertical and oblique eye movements, as delineated by electrical stimulations and lesions, project from the two sides of the brain through the diencephalon to the brain-stem.

(2) The pathways subserving horizontal movements decussate at the level of the oculomotor and trochlear nuclei, across the midsagittal plane. The direction of vector action within the brain above the 'electroanatomical' oculomotor decussation is predominately contraversive; below this level it is ipsiversive.

(3) The pontine reticular formation, the abducens and oculomotor nuclei and the median longitudinal fasciculus play an important role in the physiology of ipsilateral conjugate gaze. A 1 mm lesion within the paramedian pontine reticular formation causes paralysis of ipsilateral conjugate gaze, while a 1 mm lesion within the median longitudinal fasciculus causes impairment of contralateral (disconjugate) gaze with paralysis of adduction of the ipsilateral eye and nystagmus in the contralateral or abducting eye.

(4) True binocular vertical movements occur only when both sides of the brain are activated either directly or through bilateral sensory (visual or vestibular) inputs. Vertical and oblique monocular movements can be elicited on unilateral stimulation at the level of the oculomotor nucleus.

(5) Paralysis of vertical gaze is caused by bilateral lesions. Bilateral (1 to 2 mm) lesions within the region of the *rostral* interstitial nucleus of the median longitudinal fasciculus result in isolated paralysis of downward gaze. More caudally, bilateral (1 mm) lesions within the pretectum or midsection of the posterior commissure result in paralysis of upward gaze.

(6) In different regions of the brain a theoretical transverse plane can be drawn between pathways which transmit impulses for vertical eye movements. Those which transmit impulses for binocular downward movement are situated dorsal to

this plane, while those that transmit impulses for upward movement are located ventrally to this plane. This topographical relationship can be demonstrated in the occipital lobe and to some extent in the frontal lobes. A hypothetical transverse plane separating the down and up eye movement can also be drawn at the mesodiencephalic junction. At the level of the oculomotor nucleus stimulations at the most rostral pole result in monocular downward movements, while the most caudal pole stimulations produce monocular upward movements. There is no evidence that the pathways which mediate binocular upward and binocular downward movement project across a hypothetical transverse plane.

(7) Our knowledge of the synaptic connections between the cerebrum, diencephalon and the brain-stem nuclei, especially the paramedian pontine reticular formation, involved in binocular movements remains incomplete. Moreover, the anatomical location of the decussation of the right and left cerebral pathways which transmit conjugate eye movements are still unknown. Decussations of pathways subserving horizontal as well as vertical drives may occur through polysynaptic connections between all the ocular nuclei as well as between the pontine reticular formation on the two sides, so that there may be no one distinct massive group of crossing tracts or fibre pathways comparable to the pyramidal decussation or the crossing of the retinogeniculocalcarine pathway at the optic chiasma.

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SUPRANUCLEAR PALSY OF EYELID CLOSURE

by R. W. ROSS RUSSELL

(*From The National Hospital for Nervous Diseases, Queen Square, London WC1, St. Thomas' Hospital, London SE1 and Moorfield's Eye Hospital, City Road, London EC1*)

INTRODUCTION

VOLUNTARY eyelid closure involves the co-ordinated action of two groups of muscle fibres, contraction of the orbital and preseptal portions of the orbicularis oculi muscle and relaxation of the elevator of the upper lid. The same reciprocal activity occurs during reflex blinking induced by a corneal stimulus, loud noise or visual threat although the pretarsal portion of the orbicularis is said to contract only in reflex and in random blinking while the more peripheral parts of the muscle are preferentially activated in voluntary blinking (Gordon, 1951).

A selective loss of voluntary eyelid closure with retention of reflex activity may occur in facial dyspraxia and facial diplegia of supranuclear type. Three examples of supranuclear palsy due to cortical neuronal loss are described in patients with Creutzfeldt-Jakob's disease.

PATIENTS

Case 1

A professional musician, aged 52 years, was admitted to a psychiatric hospital for treatment of depression. He had become concerned about the falling standard in his piano technique, in particular an increasing difficulty in performing rapid finger movements with the left hand. This was not obvious to others. At about the same time he also noticed that he was having difficulty in closing his eyes, as when attempting to relax before a performance. He had to make a conscious and sustained effort to close them. He developed a habit of closing the eyelids gently with thumb and forefinger, after which the eyes would remain shut. It was observed that the eyelids closed normally in sleep.

These symptoms were considered to be psychogenic and due to a depressive reaction. He received a course of mono amine oxidase inhibitors and ECT without improvement. Neurological examination at this time confirmed the defect of voluntary eyelid closure. Reflex blinking to a bright light, visual threat, sudden noise or corneal stimulation was normal. Although having rather a fixed facial expression, spontaneous blinking was noted but the rate was thought to be reduced. Other parts of his face could be moved normally to command, as could the tongue and jaw. The jaw jerk was brisk. External ocular movements were full to command and following, his voice was normal and there were no findings in the limbs apart from unusually brisk reflexes. No clumsiness or lack of rapid finger movements could be detected. Bell's phenomenon was not tested.

Within three months there had been a clear deterioration in his physical condition. By that time mild spasticity was detectable in all limbs; finger movements (as in playing a trill) were impaired in both hands. There was facial akinesia, a slight spastic dysarthria and slowness of tongue movements. An air encephalogram showed no evidence of cortical atrophy or ventricular dilatation. Isotope brain scan was also normal. EEG was mildly abnormal but showed no features of viral encephalitis. The CSF was normal as were routine hæmatological and biochemical tests. Serology was negative.

By six months, voluntary eye movements were also involved; rapid saccadic refixation movements in the lateral or vertical planes could not be performed, although slow pursuit movements and oculocephalic movements were retained and appeared exaggerated, the patient having difficulty in changing his point of fixation. The eyelids moved downwards with down gaze. Voluntary eyelid closure was by now impossible, except with manual assistance; reflex eye closure remained normal. At this time there was also evidence of mild generalized mental impairment and emotional lability.

His condition steadily deteriorated; a year after the onset he had generalized spasticity and difficulty in moving all limbs. He had developed severe dysarthria and dysphagia. He was unable to look to either side except by turning his head, when his eyes would at first remain directed towards the previous point of fixation then slowly move to the midline. Focal muscle atrophy and fasciculation were noted around the shoulder girdle, and EMG confirmed chronic partial denervation with normal motor conduction velocity. He was able to communicate for a time using a spelling card but this ability deteriorated and he became apathetic. His infirmity increased, he became bedridden and eventually died two years after onset.

Summary. Loss of voluntary eye closure was an early symptom in this patient. Spastic facial diplegia, pseudobulbar palsy and spastic tetraparesis followed after some months. Spinal motor neuron involvement, supranuclear ocular palsy and dementia appeared only late in the disease.

Case 2

A 32-year-old motor mechanic presented with a progressive history of slowness and clumsiness affecting the right hand. Others had noticed that his speech was slurred, that his writing was slow and ill-formed and he made a number of spelling errors. There was no past or family history of neurological disease. He had been treated for gonorrhœa ten years previously.

Examination revealed a mild spastic dysarthria, slow movements of the tongue and an increased jaw jerk. Limbs had normal power but generally increased tendon reflexes and both plantar responses were extensor. There was no muscle wasting, fasciculation or sensory loss.

Air encephalography and vertebral angiography revealed no abnormality. Biochemical tests, serological tests for syphilis, CSF examination, electromyography and nerve conduction studies in the limbs were all normal. EEG showed a normal record and visual evoked potentials were of normal amplitude and latency.

His condition deteriorated; one year after onset he was having difficulty in walking and in rising from a chair because of a weakness and stiffness in both legs. His speech was more indistinct and his swallowing laboured. He also complained of loss of memory, poor concentration and difficulty in thinking of the correct word. He communicated by means of a typewriter but spelling showed a progressive deterioration. At this time he first noticed difficulty with eye movement and spontaneously complained that he could not easily transfer his gaze from one object to another. His gaze appeared to become 'locked' on the point of fixation and could be moved only by closing his eyes, turning his head and then opening his eyes again to take up the new fixation. He was unable to maintain his gaze to the extremes of lateral or upward movement, his eyes tending to return to the primary position. Voluntary movements were performed slowly. Pursuit movements were full but broken up, optokinetic nystagmus was present and convergence appeared correct. Concurrent with these features of mild supranuclear ophthalmoplegia and spasm of visual fixation there were some signs of facial involvement. He had a slight generalized facial weakness and spasticity with increased facial jerks. He was able to close his eyes, show his teeth, copy facial grimaces but could not blink rapidly to command.

His physical condition deteriorated steadily over the next few months. He became bedridden, anarthric, increasingly spastic in all limbs and incontinent of urine. He retained the ability to slowly move his eyes to command and to follow but he became quite unable to shut his eyes voluntarily. Blinking to a visual threat, to glabellar tap or to a corneal stimulus was normal. Bell's phenomenon was absent. Movements of other parts of the face were much less affected; he could show his teeth, blow out his cheeks and purse his lips. He could protrude his tongue only a short distance and the tongue movements were very slow. There were outbursts of pathological laughter and weeping.

Although his limbs were almost completely paralysed he could still spell out single words using a board. No focal muscle atrophy or fasciculation was observed. After lingering in this state for some months he finally died of bronchopneumonia four years after the onset of the illness.

Summary. Supranuclear palsy for eyelid closure developed as part of a progressive generalized spastic disorder involving the tongue, trunk and limbs. Voluntary eye movements and movements of other parts of the face were earlier affected but much less severely.

Case 3

G.P., an intelligent marketing consultant, aged 35 years, first complained of difficulty in articulation while lecturing. This was more pronounced when he tried to talk rapidly. The content of his speech was normal. At that time there was no abnormality on physical examination apart from generally brisk reflexes including a jaw jerk. His speech was slightly slurred. Psychometric testing confirmed a superior intelligence with no features of deterioration. Within two months his condition had worsened; colleagues commented on his slurred speech especially while telephoning and he had to give up lecturing and interviewing. His handwriting became less well-formed. He complained of vague mental tiredness and a tendency to emotional lability. Re-examination showed a mild spastic dysarthria and expressionless face; voluntary movements of the tongue were slow and there was hesitancy of voluntary eye closure. Ocular movements were full to command and pursuit. His limbs showed a mild spasticity and retardation of movement in the left arm. Reflexes were generally increased but the plantar responses were flexor. There was no dysphasia, no muscle wasting or fasciculation. Investigations at this time included an encephalogram and CSF investigation which were entirely normal. EEG showed mild bilateral episodes of theta waves in the posterior quadrants. Repeated psychometric examination showed a decline in performance.

His condition showed a steady mental and physical deterioration. A year after the onset he was still able to work at proof reading. Re-examination showed a supranuclear gaze palsy with marked slowness of lateral eye movements to command. Vertical movements were much less affected. Ocular movements to pursuit and oculocephalic stimuli were not impaired. He was still able to close his eyes on command but was unable to blink rapidly. Pseudobulbar palsy and weakness of the limbs were more pronounced. He remained at home but became more apathetic, forgetful and was occasionally incontinent of urine. His limbs became weaker, he had frequent falls and he had difficulty in swallowing. Speech was increasingly dysarthric. His final admission took place two years after the onset of the illness. Although correctly orientated he could not attempt simple tests of arithmetic. He was unable to speak but could communicate by writing. He was quite unable at this time to close his eyes to command, though understanding the command and attempting to close the lids with his hands (fig. 1). Bell's phenomenon was absent on each side. He was unable to wink with either eye. Blinking to a visual threat, corneal stimulation or loud noise was normal. His eyes closed during sleep. When his eyelids were gently closed by the examiner's finger he was able to open them again without difficulty. Marked restriction of conjugate ocular movements in all directions was present, following movements were normal as were oculocephalic reactions (fig. 2). He had a bilateral weakness of the lower part of the face, the tongue moved slowly and through a limited range but showed no wasting or fasciculation. The jaw jerk was increased. The limbs showed a moderate spastic quadriparesis with some doubtful wasting around the shoulder girdle. The limbs exhibited frequent jerking movements thought to be myoclonic in type involving single muscles in the upper limbs. All tendon reflexes were increased, the plantar responses were extensor. Bilateral grasp reflexes were present. EEG showed a featureless low voltage record; there was no evidence of periodic complexes. CSF examination was normal as was peripheral nerve conduction. His condition rapidly worsened; he became permanently bedridden, mute and unable to swallow and finally died in 1976 of bronchopneumonia about two years after the onset of the illness.

Summary. A progressive neurological disease in a young patient running a fatal course over two years. The main features were increasing spasticity, pseudobulbar palsy and dementia. The paresis of eyelid closure developed at the same time as the supranuclear gaze palsy. Reflex blinking was normal.

PATHOLOGICAL CHANGES

The pathological changes in the brains of these three patients were similar and were typical of Creutzfeldt-Jakob's disease. In each case there was extensive neuronal cell loss, regions of status spongeosis and of glial reaction. Spongiform change was patchy and laminar in all patients, particularly affecting layers 2 and 3 of the cortex. Gliosis was more marked in the superficial layers and was not full-thickness. Extensive pyramidal tract degeneration and myelin loss were seen in all cases. Neurofibrilliary tangles and amyloid plaques were not seen and generalized cerebral atrophy was slight. The sites of maximal involvement differed in each case and are summarized in Table 1. No attempt was made to transmit an infective agent to animals.

TABLE 1. PATHOLOGICAL FINDINGS

Case No.	*Frontal*	*Temporal*	*Parietal*	*Occipital*	*Basal ganglia*	*Cerebellum*	*Brain-stem*	*Spinal cord*
1	Sp +	—	+ +	+	—	—	—	—
	NL + + +	—	+ +	+	+	—	—	+
	GL + + +	—	+	+	+ +	—	—	+
							Myelin loss	Myelin loss
2	Sp + + +	+	+ +	+	—	—	—	—
	NL + + +	+	+ +	+	—	—	—	—
	GL + + +	+	+ +	—	—	—	—	—
							Myelin loss	Myelin loss
3	Sp + + +	+ +	+	+ +	+ +	+	+ + + (patchy)	—
	NL + +	+	+	+	+ + +	+ +	+	+
	GL + + +	+	+	+ +	+ + +	+ +	+ +	+
							Myelin loss	Myelin loss

+ = mild. + + = moderate. + + + = severe. Sp = spongiform change. NL = neuronal loss. GL = gliosis.

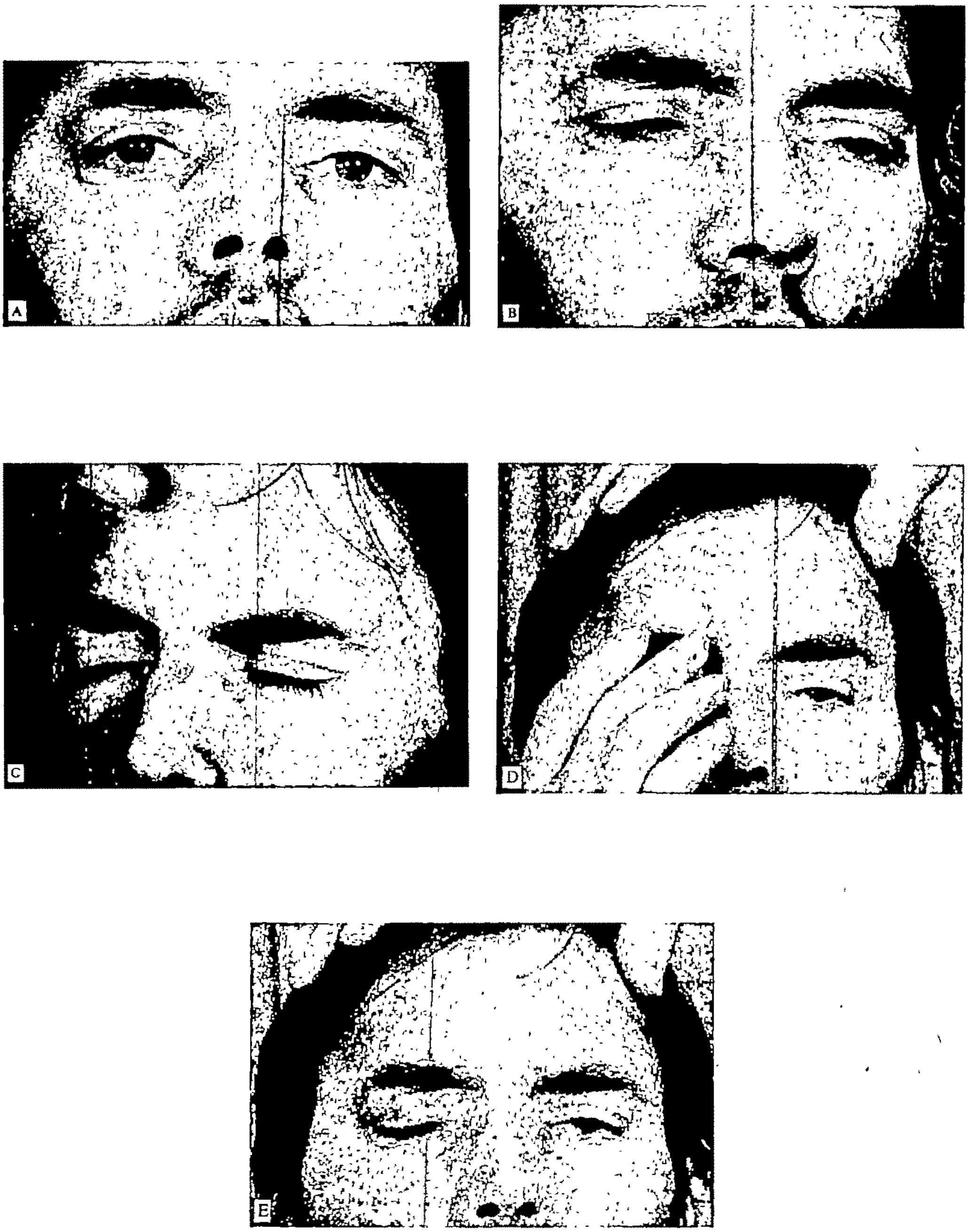
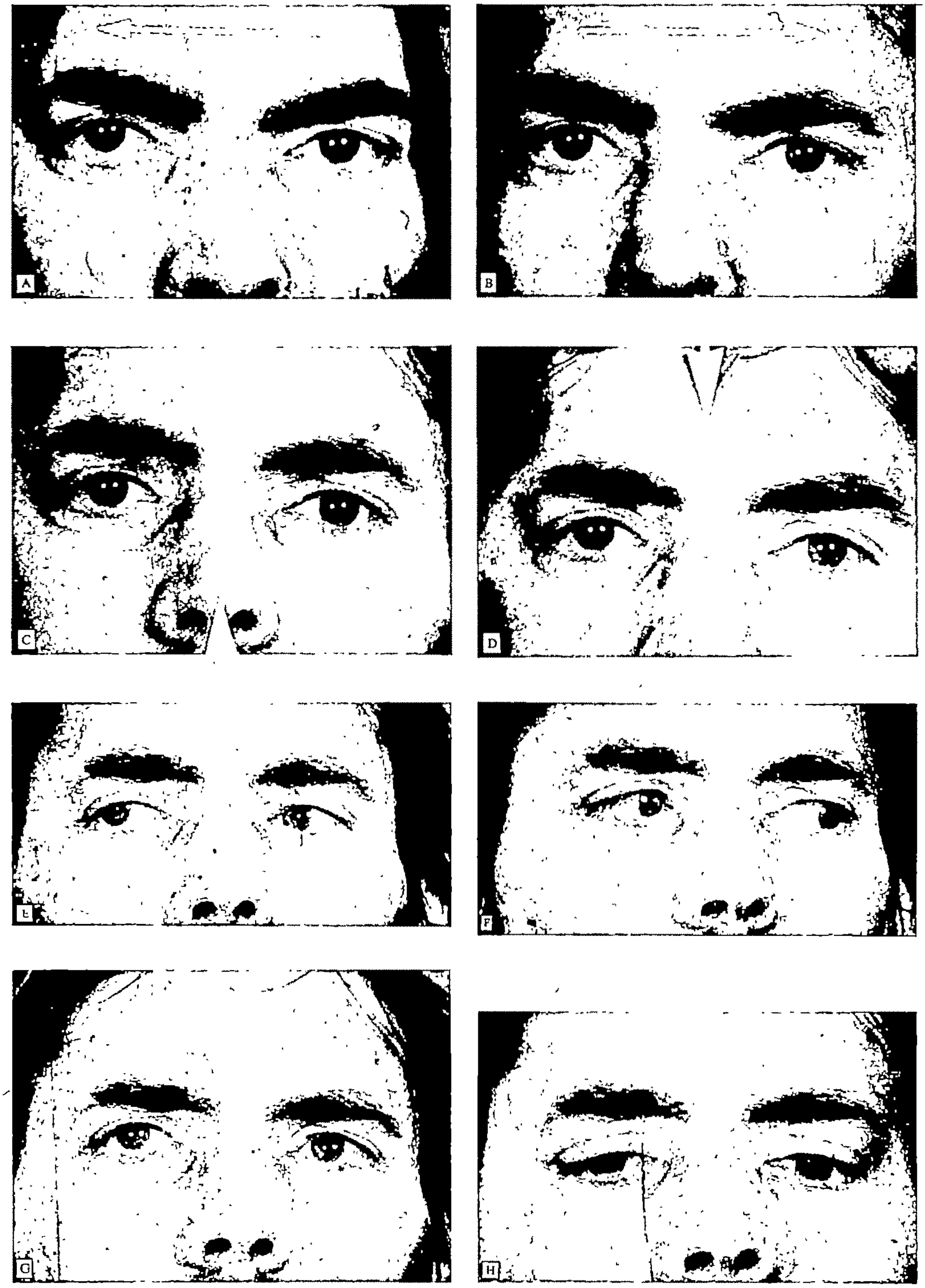


FIG. 1. *Case 3*—eyelid closure (six months before death). A, attempted voluntary eye closure on command. B, blinking to a visual threat. C, blinking to glabellar tap. D, attempting to close eyelids digitally. E, a random blink.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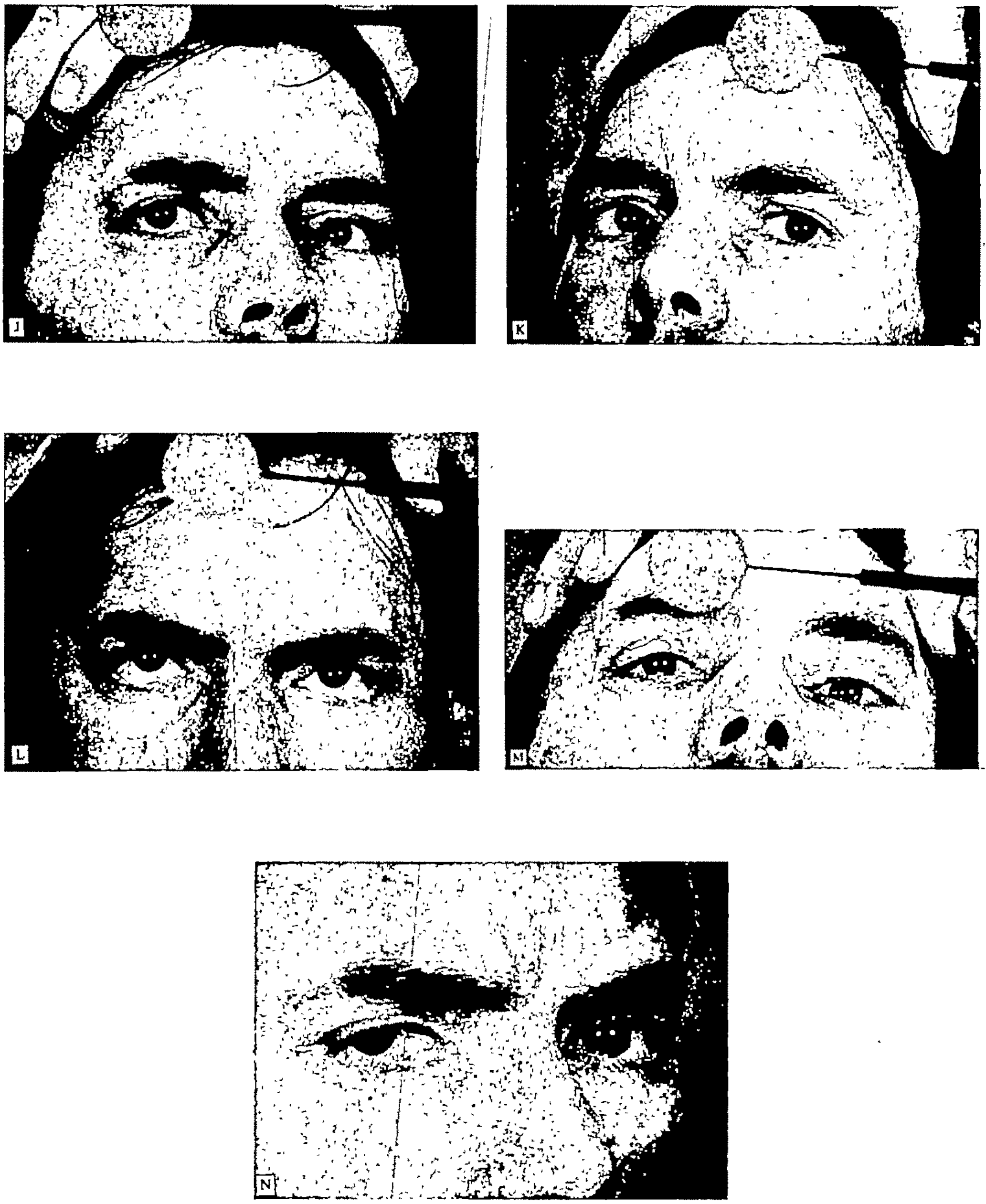

FIG. 2. *Case 3*—ocular movements. A–D, attempted gaze to right, left, up and down. E–H, slow pursuit movements right, left, up and down. J–M, oculocephalic movements during ocular fixation. N, random eye movement.

DISCUSSION

The three patients had a number of clinical features in common: all exhibited a dementia progressing to a fatal outcome in two to four years. All showed marked motor involvement of pyramidal type eventually affecting facial, bulbar, axial and limb muscles. In addition there was spinal motoneuron involvement in Cases 1 and 3. The pathological findings were similar and consistent with Creutzfeldt-Jakob's disease.

The clinical features included one not often encountered in patients with supranuclear palsy, a paresis of voluntary eyelid closure with retention of normal reflex blinking. This was an early symptom in Case 1, occurring at a time when there was minimal involvement of the limbs and when no disturbance in voluntary movements of the eyes, mouth, tongue or pharynx could be detected. In Cases 2 and 3 the failure of eyelid closure occurred later, in the setting of a generalized spasticity including a pseudobulbar palsy. A supranuclear ophthalmoplegia also developed in the course of the disease although this varied considerably in severity.

The evolution of the eyelid disorder can be traced in the three patients. In the early stages the patient may be unable to perform a rapid series of blinks while a single sustained eye closure can still be achieved. Voluntary eyelid closure gradually becomes more slow and incomplete until finally the maximum effort produces no detectable narrowing of the palpebral fissures. At the same time there is retention of normal reflex blinking to corneal stimulation, to visual threat or to emotional stimuli, and random blinking continues, although at a reduced rate. During sleep the eyes close normally. When vertical eye movements are executed the upper lids descend normally on downward gaze and show no unusual lag or retraction. Indeed the patient may use a rapid downward movement of the eyes or extension of the neck as a means of initiating eyelid closure when he cannot achieve the movement voluntarily. Sometimes the patient may resort to closing the lids with the finger-tips. Once closed the eyelids appear normal, there is no blepharospasm and closure can be maintained indefinitely. Opening of the eyelids presents no difficulty.

This syndrome has been previously described in a few patients with bilateral occlusive vascular disease producing a pseudobulbar palsy (Alajouanine and Thurel, 1933) and caused by bilateral cortical infarcts of the Rolandic operculum. It has also been reported in advanced motor neuron disease (Lapresle and Salisachs, 1976). In most of the reports there has been simultaneous involvement of other facial, jaw, tongue and pharyngeal muscles, although not necessarily of the limbs.

In Creutzfeldt-Jakob's disease a spastic paresis with or without features of extra-pyramidal, cerebellar or spinal cord involvement may be seen in company with a generalized and progressive dementia (Beck, Daniel, Matthews, Stevens, Alpers, Asher, Gajdusek and Gibbs, 1969). Although supranuclear gaze palsy is well recognized, paresis of voluntary eyelid closure has not been previously included in the clinical descriptions of this disease, possibly because the sign may be overlooked in severely paralysed and demented patients.

It is curious that the defects in eyelid closure of cerebral origin are so uncommon. The relative sparing of the upper half of the face in unilateral hemisphere lesions is classically explained by the fact that fibres from that region of the motor cortex concerned with movements of the forehead and orbicularis oculi decussate only partially in the upper brain-stem so that the facial nuclei receive innervation from both hemispheres. This is supported by observations during localized electrical cortical stimulation in both primates and man (Foerster, 1936; Penfield and Rasmussen, 1950). Minimal stimulation in the appropriate region in the precentral gyrus (which is below that concerned with ear, nostril, neck and lip and adjacent to the thumb area) causes closure of the opposite eye but as the stimulus intensity is increased both eyes become involved (Leyton and Sherrington, 1917).

A patient who has had a stroke, either resulting from a cortical infarct in the middle cerebral territory or from a more localized infarct in the capsular region, can usually close both eyes without difficulty, although the force of eyelid closure is less on the paretic side, and the patient may be unable to wink the eye (Ehlers, 1929). Bilateral lesions might be expected to involve all parts of the face including the forehead and orbicularis oculi. It appears, however, that in vascular pseudobulbar palsy resulting from bilateral capsular lesions the ability to close the eyes is almost always retained although the whole of the face may be weak and spastic and speaking, chewing and swallowing may be virtually abolished. It may be that extensive bilateral damage to the neurons of the motor cortex is more likely to produce the syndrome than lesions primary involving subcortical white matter or descending tracts. This would be in keeping with the pathology of Creutzfeldt-Jakob's disease and also of severe motor neuron disease (Smith, 1960).

Case 1, in whom the defect of eyelid closure was such an early and striking symptom, presumably had fortuitous bilateral involvement of a patchy kind of the relevant cortical regions while surrounding regions concerned with movements of the eyes, other parts of the face, jaw and pharynx escaped damage until later in the disease. In Cases 2 and 3 defective eye closure occurred as a later feature in company with involvement of other parts of the face and with generalized spasticity of the limbs.

Failure of eyelid closure may also occur as part of a true facial dyspraxia with defective voluntary control of the face, jaw, tongue and larynx but with retention of normal spontaneous movements including blinking. This is encountered occasionally as a variety of developmental dyspraxia and is usually associated with generalized mental retardation. According to Geschwind, unilateral lesions in the region of the supramarginal gyrus of the dominant hemisphere may cause facial apraxia by interfering with the connections between visual and auditory cortex and the association area under the motor face area. Localized lesions of the prefrontal gyrus which have also been reported to cause dyspraxia of face, tongue and speech

(Nathan, 1947) may do so either by destroying the subcortical association area or by destroying the face area itself with its projections, including those in the corpus callosum. In the above descriptions of facial apraxia, although the abnormalities of movement of lips, mouth and tongue are emphasized, eyelid closure receives little attention.

In the present context the existence of a true dyspraxia for facial and eyelid movements can only be established if random blinking and normal facial mobility are present and of normal velocity and frequency. Although the rates of blinking were unfortunately not studied systematically it was noted clinically that blinking occurred less frequently than normal and that spontaneous facial movements were reduced. Furthermore no spontaneous random rapid eye movements were observed in Patients 1 and 3 at a time when they had a severe ophthalmoplegia.

For these reasons and because of the accompanying spasticity of bulbar limb muscles, it seems preferable to regard the defect of eyelid closure as a variety of supranuclear palsy caused by loss of the cortical motor neurons in the facial areas of the motor cortex on both sides.

The retention of normal reflex blinking to corneal stimulation or to noise is not unexpected since this depends on an intact brain-stem. However, the retention of normal reflex blinking to a visual threat was noted in the present series and in other reports (Alajouanine and Thurel, 1933) suggest that this reflex relies only on an intact occipitopontine pathway and does not involve the frontal cortex.

Two other features described in association with severe supranuclear lesions of the facial and ocular muscles were also noted in the present patients. These are an absence of the normal conjugate upward movement of the eye on eyelid closure (Bell's phenomenon) and a difficulty in transferring gaze quickly from one point of fixation to another (spasm of conjugate gaze).

Bell's phenomenon is a sign of limited clinical value since it may be absent in a proportion of normal patients, the proportion varying widely according to the techniques used to elicit it. Cogan (1965) has described asymmetrical deviations of the eyes during Bell's phenomenon in patients with unilateral lesions of the frontopontine pathway. The eyes deviate towards the side of the lesion due to the tonic unopposed action of the normal hemisphere (spasticity of conjugate gaze). Complete absence of any upward movement has recently been described in a number of patients with advanced amyotrophic lateral sclerosis (Esteban, Andres and Gimenez-Rotdan, 1978).

A difficulty in transferring gaze from one point to another in the lateral plane is a more reliable sign with a notable history having been first described by Gowers (1879) a century ago and analysed by Denny-Brown (1977). It is due to bilateral lesions of the frontopontine pathways. Its earliest feature is a diminished control over the voluntary initiation and execution of lateral eye movements which become slower, irregular and ill-sustained. Electrical recording shows a reduction in the normal velocity of saccadic movement (saccadic paresis—Starr, 1967). The condition usually progresses until voluntary movements are entirely lost; slow pursuit is normal, vestibular and oculocephalic movements are retained though without the saccadic component. Bilateral saccadic paresis releases the normally latent occipital fixation and pursuit reflexes which depend on the integrity of the occipital lobes and their projections to the brain-stem. Bilateral frontal lesions appear to release the pursuit reflex in an exaggerated form so that the patient cannot readily transfer his gaze from one point of fixation to another, a sign named 'spasm of fixation' by Holmes (1930). Case 1 noticed this difficulty which was confirmed on examination, but voluntary eye movements were not tested in the absence of fixation. Electrical recording of the eye movements was not performed. This makes the point, emphasized by Holmes but forgotten in most textbooks of clinical examination, that voluntary rapid eye movements should be tested in two ways, first, by asking the patient to make fast eye movements in front of a blank wall (without fixation) and secondly, he should be asked to transfer his gaze rapidly from one point to another. Some patients with spasm of fixation learn to shift their gaze by closing the eyes with one or more blinks (thus abolishing fixation), turning the head and opening the eyes again (Hoyt and Darroff, 1971).

SUMMARY

An inability to close the eyes voluntarily while at the same time retaining reflex blinking is described in three patients with Creutzfeldt-Jakob's disease. In one patient it was an early symptom but in the others it formed part of a generalized spastic paralysis. By analogy with other reports it is deduced that in the case of a supranuclear palsy of this type the site of the lesion is probably in the cortical neurons rather than in the descending motor tracts.

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VISION IN THE TEMPORAL CRESCENT IN OCCIPITAL INFARCTION

by SARAH BENTON, IVOR LEVY *and* MICHAEL SWASH

(*From the Section of Neurological Sciences, The London Hospital, London E1 1BB*)

INTRODUCTION

THE temporal crescent is a peripheral unpaired portion of the visual field which extends between 60 and 100 degrees from fixation in the horizontal meridian (Traquair, 1927). Little attention has been given in recent years to sparing or impairment of vision in this monocular part of the visual field. Selective impairment of the temporal crescent is rare (Kronfeld, 1932; Bender and Kanzer, 1939), although first described by Delepine in 1890. Sparing of the temporal crescent in patients with hemianopia or quadrantanopia is an ill-recognized phenomenon. Harris (1897) and Bramwell (1899) reported several patients with occipital lesions in whom the temporal crescent was spared and Poppelreuter (1917) and Holmes (1918) described further instances in their studies of penetrating injuries of the striate cortex. Riddoch (1917) found that in some patients with hemianopias resulting from occipital lesions movement perception was relatively spared. In one of these patients perimetry showed that the temporal crescent was spared and in some of the others a residual ability to perceive movement was particularly evident in this part of the apparently blind field.

In this paper we shall describe four patients with hemianopias due to occipital infarcts. In each of these patients there was useful vision in the temporal crescent and, in particular, their ability to perceive moving stimuli in this part of the field was strikingly spared. These observations have prompted us to reconsider the functional significance of this part of the visual field in man.

PATIENTS

Case 1 (LH 788178)

A 57-year-old man was admitted for investigation of a persistent visual disturbance. During adolescence he had experienced frequent attacks of classical migraine. These always began with an aura of scintillating wavy lines in the central field of both eyes. During a period of twenty minutes the area of scintillation enlarged and moved into the right upper quadrant of his field. It usually terminated in a severe unilateral headache. The migrainous attacks ceased when he was about 20 years old. Six months before admission he suffered a mild, migraine-like attack, consisting of a sudden headache accompanied by impaired vision on the right side. The headache subsided in a few

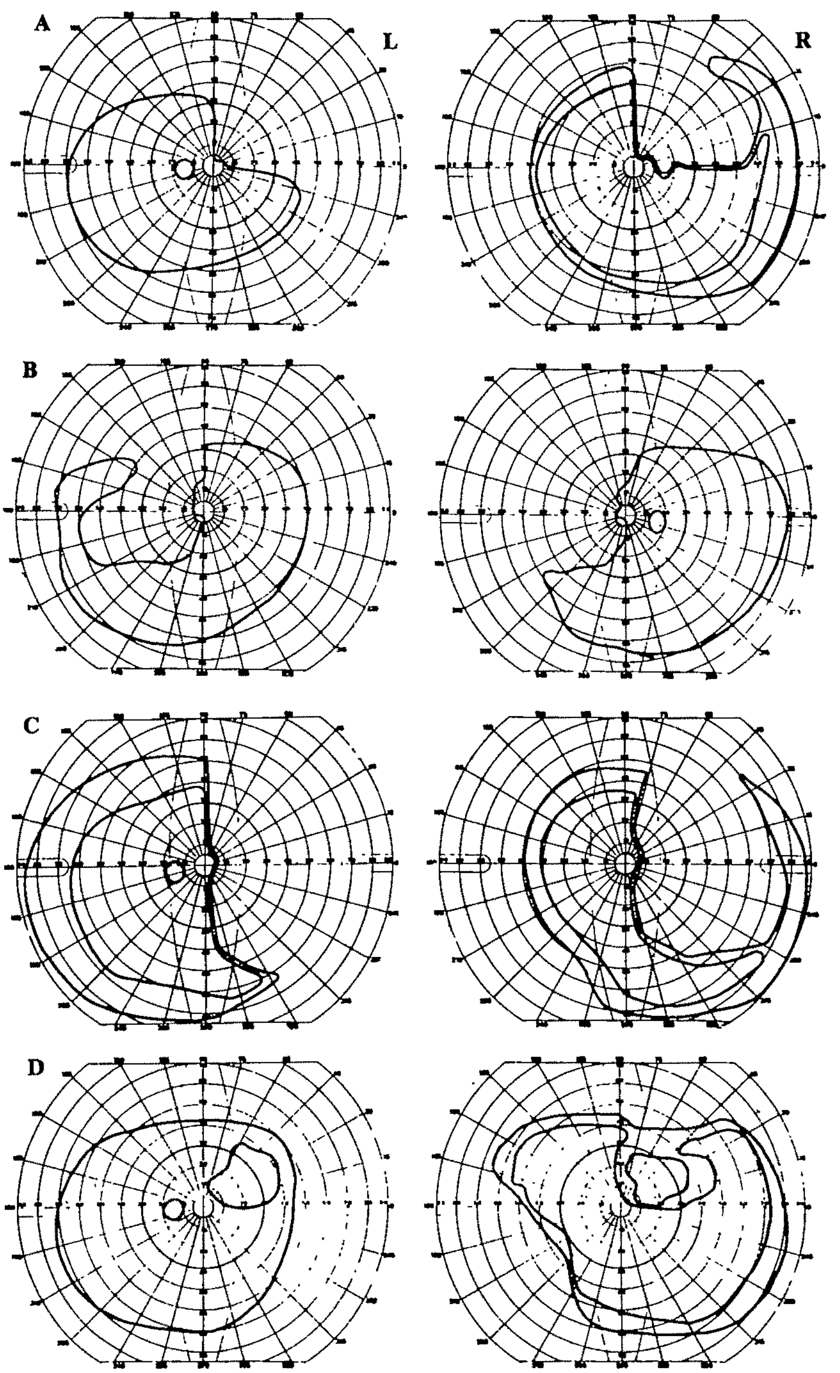

FIG. 1. Visual fields, charted with a Goldmann perimeter. A, *Case 1*—target, 1430 lux, subtending 1 deg. 33 min. at cornea. B, *Case 2*—target, 1430 lux, subtending 1 deg. 33 min. at cornea. C, *Case 3*—targets, both 1430 lux, subtending 1 deg. 33 min. and 0 deg. 10 min. at cornea respectively. D, *Case 4*—targets, both 1430 lux, subtending 1 deg. 33 min. and 0 deg. 10 min. at cornea, respectively.

hours, but he noticed that an area of shiny, moving lines, exactly like his previous migraine, was still present in his right upper field. This persisted, but he experienced no further headache. Later that day he noticed that although he could see things coming towards him from his right, they tended to disappear before suddenly reappearing in front of him. His ability to read and to write was unimpaired and he had continued working during the six months before he sought advice. Five years previously he had been treated for a myocardial infarct.

On examination there was a homonymous right upper quadrantanopia to confrontation. He was able to delineate the area occupied by an iridescent positive scotoma within this blind zone. Testing with finger movements, and with a Goldmann perimeter, revealed a temporal crescent of preserved vision (fig. 1A). Although he could perceive and localize moving objects within this preserved temporal crescent with precision, he could not recognize them or describe their shape or colour, even in quite bright illumination, unless they were very large. He could, however, accurately count slowly moving fingers in the temporal crescent. The visual acuity was 6/6 bilaterally. Following and saccadic extra-ocular movements were normal and optokinetic nystagmus was symmetrical to left and right. His ability to read, to recognize objects and to discern their spatial relationships was normal. There was no abnormality of line bisection and he could distinguish and name objects in Poppelreuter's diagram without difficulty. Tests of drawing and figure copying revealed no abnormality. When walking in an unfamiliar environment he showed no difficulty in orientating himself and he was equally aware of the extreme obstacles to his right and left. He learned the geography of the ward and of the hospital rapidly and accurately. The general neurological examination revealed no abnormality in the other cranial nerves, or in the limbs; both plantar responses were flexor. Computerized axial tomography (CT scan) of the head revealed a deeply situated lesion of low attenuation in the mesial part of the left occipital lobe, consistent with an infarct (fig. 2).

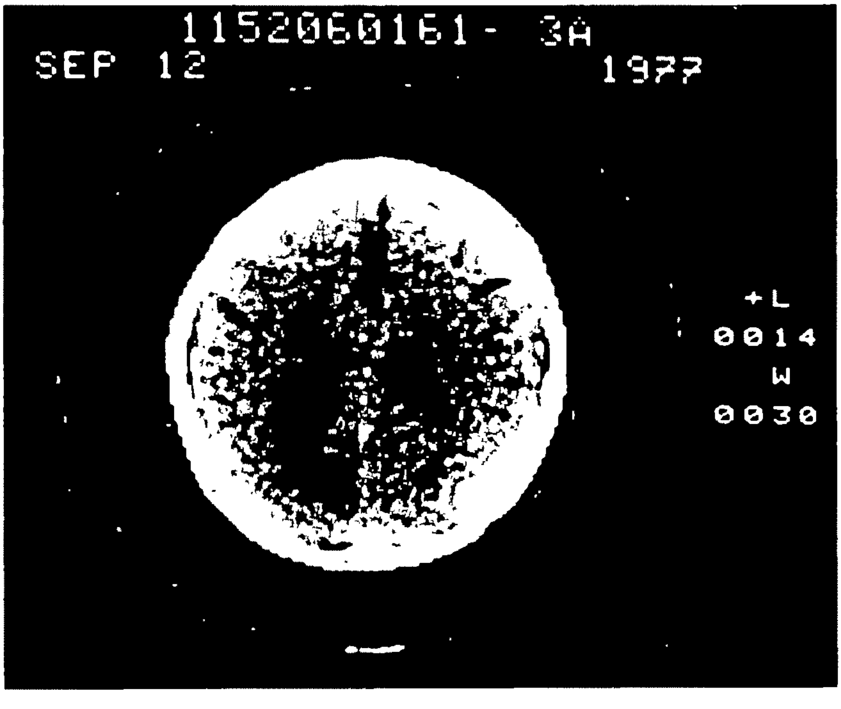

FIG. 2. CT scan in Case 1. There is a deeply situated lesion of low attenuation, consistent with infarction, in the mesial part of the left occipital lobe.

Case 2 (*LH 789146*)

A 58-year-old man was awoken an hour earlier than usual by a severe headache. The headache resolved in about twenty minutes and he went back to sleep. When he awoke two hours later he noticed that he could not see to his left and he thought that the sunlight seemed unusually bright. Later that day he realized that although he could see impressions of people or vehicles moving towards him far to the left in his blind field, he lost them as they approached him and he sometimes had difficulty finding them again before they appeared in front of him. He could only recognize moving objects themselves in his far left visual field if they were very large and familiar, for example, a car. Despite these symptoms he was able to get about normally and to continue working. His reading and writing were normal.

On examination there was a homonymous left upper quadrantanopia with preservation of the temporal crescent to moving fingers and on Goldmann perimetry (fig. 1B). The visual acuity was 6/6 in both eyes. Optokinetic nystagmus and saccadic and pursuit external ocular movements were normal. A full clinical assessment of other visual and spatial functions, as in Case 1, revealed no abnormality. For the first few days there was a positional nystagmus to the left, accompanied by vertigo, but this rapidly improved. A CT scan revealed an area of low attenuation, which showed vascular enhancement after intravenous contrast, in the mesial part of the right occipital lobe (fig. 3).

Case 3 (*LH 408608*)

For a year before the onset of her neurological disorder this 51-year-old woman had been treated with an oral contraceptive drug because of irregular menstrual periods. Three months before admission she experienced sudden episodes of numbness of the right side of her face, associated with

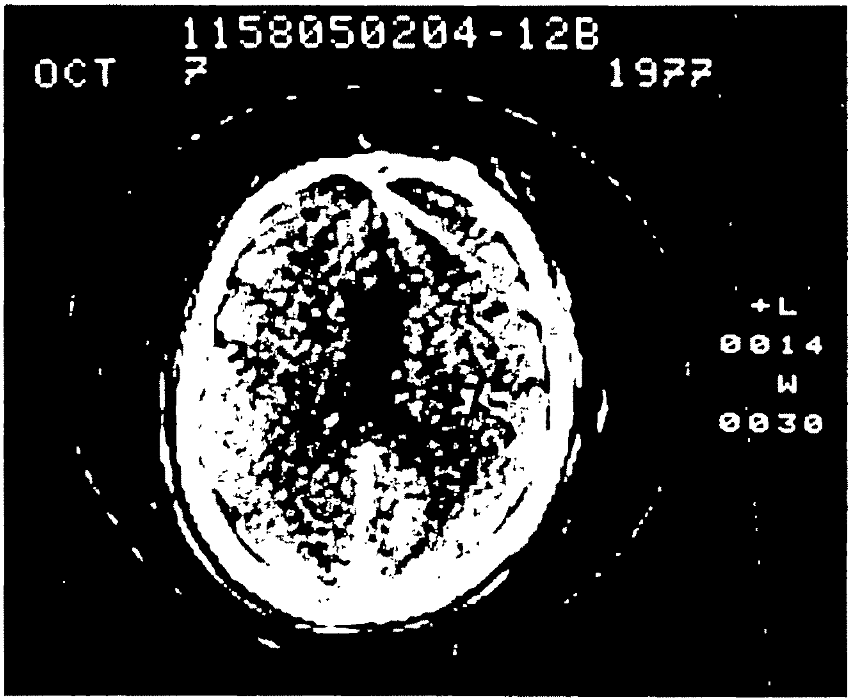

FIG. 3. CT scan in Case 2. Enhancement of a lesion of low attenuation after intravenous contrast. The lesion is situated in the right occipital lobe.

twitching of her right arm and leg. The episode lasted about five minutes and recovery seemed to be complete. However, two months later, looking in her mirror, she suddenly realized that she could not see to her right. When examined three weeks later she was found to have a right homonymous hemianopia, with preservation of the temporal crescent both to finger movement and on Goldmann perimetry (fig. 1C). The visual acuity was 6/6 bilaterally. Both saccadic and pursuit ocular movements appeared normal, and optokinetic nystagmus was symmetrical to left and right. There was no impairment of reading, writing or drawing and other tests of orientation in visual space, as in Case 1, revealed no abnormality. Bilateral subclavian bruits were detected, but there was no other clinical abnormality. A CT scan showed a zone of low attenuation, consistent with infarction, in the mesial part of the left occipital lobe (fig. 4).

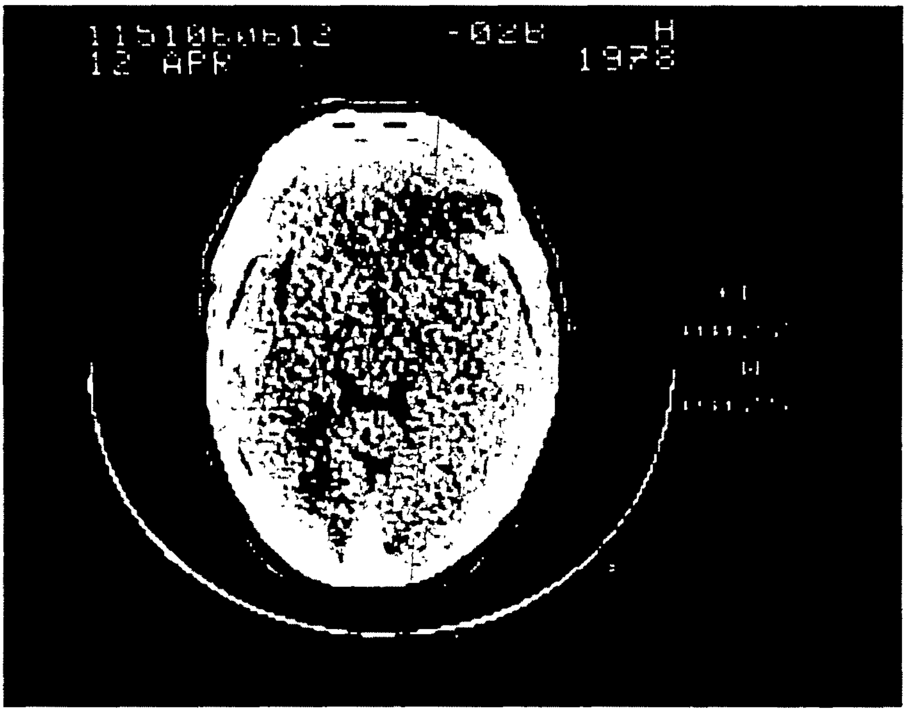

FIG. 4. CT scan in Case 3. There is a lesion of low attenuation, consistent with infarction, in the anterior and mesial part of the left occipital lobe.

Case 4 (*LH 380311*)

This 51-year-old man was admitted for investigation. Four weeks previously he had suddenly lost his memory while at a party. He was taken home and had no subsequent recollection of events until the following morning. He complained of a poor memory for recent events and that he had difficulty in reading, although he could speak and write normally. Four years previously he had suffered a myocardial infarct.

On examination there was mild left supranuclear facial weakness with an incomplete right homonymous hemianopia. The temporal crescent was preserved to finger movement and vision could also be demonstrated in the crescent with Goldmann perimetry (fig. 1D).The visual acuity was 6/6 in both eyes. External ocular movements were normal, but, in response to stimuli approaching from the

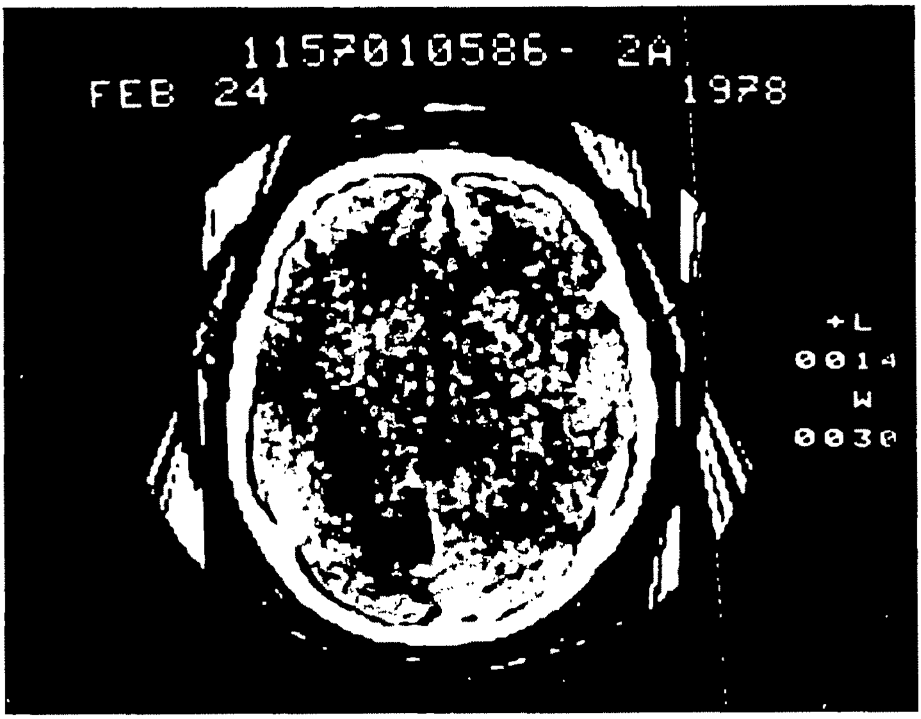

FIG. 5. CT scan in Case 4. A large infarct is seen as a zone of low attenuation in the left occipital and parietal regions. The lesion does not enhance after intravenous contrast.

right, optokinetic nystagmus was poorly developed. When asked to bisect a line, he consistently displaced the centre of the line to the right. Tests with Poppelreuter's diagram showed neglect of objects on the right of the figure and, when shown half figures, with the absent half figure orientated in the hemianopic field, completion occurred. Tests of drawing and figure copying suggested that these abilities were impaired. There was dyslexia without dysgraphia or aphasia. There was no defect in colour naming. There were no dysphasic errors in his attempts to do the verbal tests of the Wechsler Adult Intelligence Scale. However, he appeared to have a selective verbal memory deficit. On a recognition memory test for words he scored at the defective level. In a recognition memory test for visual material his score was average; verbal retention tested by cued recall was borderline, but verbal retention tested by yes/no recognition was extremely poor (Dr Elizabeth Warrington).

A CT scan revealed a deep, left parieto-occipital zone of low attenuation, consistent with infarction, which extended, in addition, into the splenium of the corpus callosum (figs. 5 and 6).

DISCUSSION

In each of these four patients with homonymous hemianopias or quadrantanopias the temporal crescent was spared. In each case the clinical and radiological features were consistent with occipital infarction. The lesions demonstrated by CT scanning were circumscribed, but involved the deep occipital white matter in

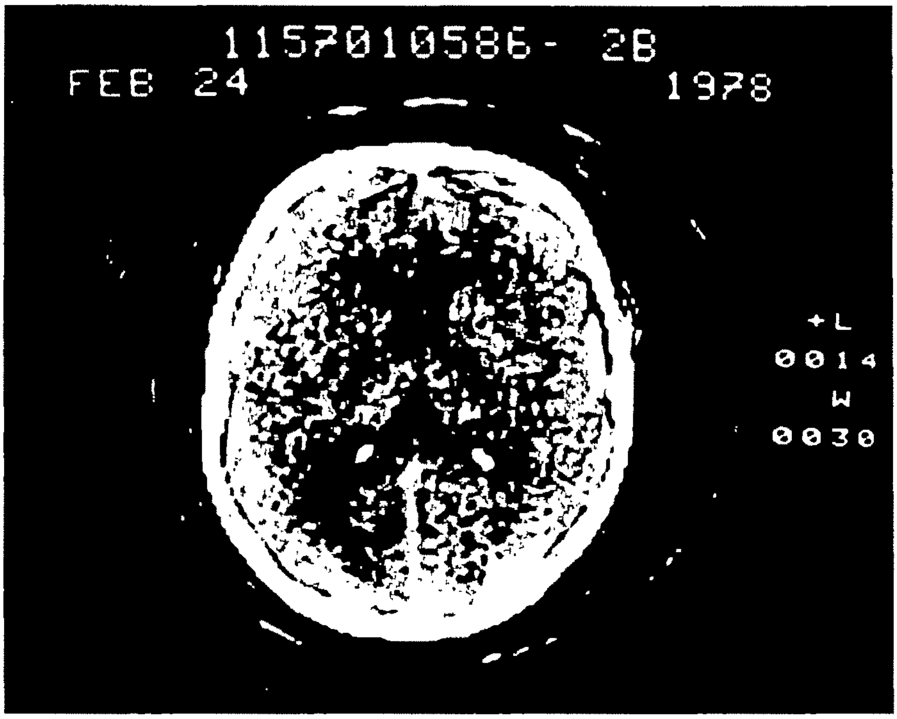

FIG. 6. CT scan in Case 4. In this slightly higher cut the lesion extends into the splenium of the corpus callosum. The posterior horn and the body of the left lateral ventricle are slightly dilated. The lesion shows no enhancement with contrast.

addition to the mesial occipital cortex. In Case 4 the lesion extended forward into the parieto-occipital white matter and into the splenium of the corpus callosum, and in this patient there were additional clinical features, including defective verbal memory, alexia, disturbed figure drawing and impaired optokinetic nystagmus, consistent with this more anteriorly situated lesion. One patient (Case 1) experienced a persistent hallucination of iridescent moving lines in the blind area of his field. Horrax and Putnam (1933) noted that similar unformed hallucinatory images were common in patients with occipital tumours. Formed visual hallucinations, a feature of patients with more anteriorly situated lesions (Cushing, 1922; Lance, 1976), did not occur in any of our patients. In three patients (Cases 1, 2 and 4) the cerebral lesions were thought to be embolic and in the remaining patient (Case 3) treatment with an oral contraceptive drug may have played a role.

Anatomical studies have shown that the most peripheral part of the temporal field, the temporal crescent, is unpaired and therefore unilaterally represented in the striate cortex. Brouwer and Zeeman (1926) traced the path of these fibres from the nasal part of the retina to the lateral geniculate body and Poliak (1932) followed them to the calcarine cortex. Traquair (1927) suggested that fibres from the temporal crescent occupied the mesial part of the geniculo-striate radiation. Pfeiffer (1925) thought that these fibres reached the occipital cortex by passing the posterior horn of the lateral ventrical inferiorly, but Poliak (1932) showed that they passed both above and below this part of the ventricular system. Holmes (1918) indicated that the monocular temporal crescent was represented in the most anterior part of the striate cortex, the upper half of the crescent situated in the lower lip, and the lower half in the upper lip. Poliak (1932) however, represented the temporal crescent only in the inferior lip of calcarine cortex. Subsequent work in the chimpanzee (Spence and Fulton, 1936) also suggested that the temporal crescent is represented in the most anterior part of the inferior lip of the calcarine fissure.

The striate cortex is supplied by calcarine, posterior temporal and parieto-occipital branches of the posterior cerebral artery and by occipital branches of the anterior cerebral artery. Smith and Richardson (1966) have pointed out that there are several different patterns of dominance of these four vessels in the blood supply of the striate cortex and have shown that this variability can account for different types of field defects. In all our patients the temporal crescent arose from the inferior quadrant of the field and extended superiorly towards the midline (fig. 1), indicating that the lower lip of the striate cortex or its underlying white matter was more involved than the upper lip. In earlier reports of sparing of the temporal crescent (Harris, 1897; Bramwell, 1899; Kronfeld, 1932), the crescent usually arose from the superior quadrant, but in those patients the occipital lesions were of varied ætiology. Many were due to occipital missile wounds (Riddoch, 1917; Poppelreuter, 1917; Holmes, 1918). Since patients receiving wounds involving the inferior lip of the striate cortex rarely survive, because of associated injury to the torcula, one would expect the survivors of occipital penetrating injuries to show predominant signs of injury to the upper lip of the striate cortex.

In our patients the lesions shown by CT scanning involved occipital white matter in addition to the striate cortex itself. Putnam (1926) showed that the geniculostriate projection within the occipital lobe is arranged in lamellæ representing different parts of the retinotopic field (Holmes, 1918); the fibre bundles entering the striate cortex most anteriorly contain fibres derived from nasal retinal cells representing the unpaired temporal crescent. The lesions in our patients were probably all sufficiently far posterior, and in Case 4 sufficiently superior, for these fibres to be spared, although those fibres representing the paired paracentral fields were damaged (*see* fig. 7). The macular fibres were spared in our patients (fig. 1), a common finding in occipital infarction, probably due to the different blood supply of the tip of the occipital lobe.

None of our patients' fields showed a homologous nasal crescent, although in Case 3 there was a small area of preserved vision extending 30 radians into the blind nasal field of the left eye. In this patient's right eye there was a narrow peripheral temporal crescent of residual vision. There seems no doubt that the they turned their gaze towards the moving stimulus the object disappeared and was sometimes difficult to find. Difficulty in locating objects perceived in the temporal crescent is not surprising since to bring these objects into the foveal field would require a saccadic movement of more than 60 degrees; saccades are rarely greater than 30 degrees and a movement of this extent would result in the object becoming 'lost' in the blind part of the field. The moving images perceived in the peripheral field were described as being 'like shadows'. They did not have clearly defined form or colour and they could not usually be recognized. However, they were localized accurately. Both these patients had noted that static stimuli in this peripheral part of the field were not always perceived unless they were very brightly illuminated. Acuity in the temporal crescent was thus poor, but our patient (Case 1) could count slowly moving fingers in the preserved temporal crescent.

Our patients were able to direct their eyes towards peripheral moving stimuli, indicating that they could generate saccades as part of their fixation reflex. A further test of saccadic oculomotor control is optokinetic nystagmus; in Cases 1, 2 and 3 optokinetic nystagmus evoked in response to stimuli moving across the field from the side of the preserved temporal crescent appeared similar, but opposite in phase, to that produced by contralateral testing. Saccadic control depends both on geniculo-striate and, probably, on a non-striate mesencephalic projection from geniculate or pregeniculate fibres (Mohler and Wurtz, 1977). Interpretation of the functional significance of these two possible pathways in the control of human saccadic eye movements is controversial. In Case 4 optokinetic nystagmus was asymmetrical, line bisection was abnormal and the completion phenomenon (Warrington, 1962) was present. These signs were consistent with the finding on the CT scan that the lesion extended into the parieto-occipital cortex and the splenium of the corpus callosum. In none of the other patients were these signs present.

Ikeda and Wright (1972) have suggested, in the cat, that the perception of stationary patterns and of movement is achieved by separate mechanisms, and have postulated that different populations of cells are concerned with the detection of a pattern and its movement. These two cell populations have been termed sustained, or X, cells, and transient, or Y, cells. Transient cells are very sensitive to changes in the pattern of illumination over their receptive fields produced, for example, by a moving object in the peripheral visual field. These peripheral 'attention-getting' moving stimuli initiate the fixation reflex. This reflex allows the object of interest to be directed to the fovea so that its spatial detail can be analysed by the sustained X-cell pathway. The proportion of transient cells increases steadily towards the periphery of the retina (Ikeda and Wright, 1972). Sustained and transient neurons also exist in primate visual systems (Gouras, 1969) but the cortical representation of these systems is not known. Our observations regarding movement perception in the periphery of the field in patients known to have lesions of the striate cortex and Riddoch's (1917) description of spared movement perception in patients with hemianopias to static stimuli, suggest that this area represents one cortical projection of the transient cell system.

Riddoch (1917) described a number of patients with occipital penetrating injuries who could recognize movement in their apparently blind fields. In one of his patients there was a full field for moving fingers, but 'a complete homonymous hemianopia to perimetry with a one-centimetre object'. In some of his other patients this dissociation between the perception of moving and more nearly static stimuli was less complete. Holmes (1918) thought that this apparent dissociation was due to reduced acuity in the affected field, rather than evidence for separate pathways for stationary and moving stimuli. Our observations on vision in the temporal crescent are similar to those of Riddoch in that he also noted that the temporal crescent, when preserved in patients with occipital lesions, was particularly important in perception of movement. For example, in one of his patients moving stimuli in the upper temporal crescent could be accurately localized although, as in our patients, form and colour could not be perceived. Our patients perceived finger movements only in their preserved temporal crescents and not, as in some of Riddoch's (1917) cases, in the whole hemianopic field.

It has been known since Riddoch's (1917) and Holmes' (1918) work on the cortical representation of vision in man that some visual function may be retained in patients with occipital lesions, and the nature of this residual visual capacity has recently been the subject of renewed interest. Riddoch's and Holmes' work was largely based on patients with penetrating occipital brain injuries but in man the anterior part of the striate cortex is buried in the anterior part of the mesial aspect of the occipital lobe, and is therefore relatively protected from injury. Our patients' visual fields show that this part of the striate cortex may also be spared in occipital infarction. The question therefore arises as to whether sparing of the temporal crescent might account for part of the residual visual ability found after occipital lesions in man; as in the patients described by Pöppel, Held and Frost (1973), Weiskrantz, Warrington, Sanders and Marshall (1974) and Perenin and Jeannerod (1975). Indeed, residual vision was detected in the temporal crescent by perimetry in the patients described by Pöppel *et al.* (1973) and by Perenin and Jeannerod (1975), and a small island of preserved vision is illustrated in the paper by Weiskrantz *et al.* (1974), describing a patient with 'blind-sight'. Humphrey (1974) recognized this possibility in his discussion of the nature of the residual visual ability of a monkey, Helen, in whom most of the striate cortex had been excized, but rejected it. In man, spatially directed responses to brief flash stimuli, applied in apparently blind parts of hemianopic fields, have been studied by Pöppel *et al.* (1973), Weiskrantz *et al.* (1974) and by Perenin and Jeannerod (1975). Accurate responses were elicited in the apparently blind fields of these patients *mesial* to 60 degrees, that is, mesial to the monocular temporal crescent and, in one case, peripheral to 60 degrees (Weiskrantz *et al.*, 1974). In similar experiments in the monkey after striate ablation (Humphrey, 1974; Weiskrantz, Cowey and Passingham, 1977) spatially directed responses were found to brief flash stimuli over the whole of the hemianopic field. In one of these monkeys the striate lesion was shown to be complete with degeneration of *all* the neurons in the lateral geniculate body (Weiskrantz *et al.*, 1977) an observation which excludes any role of the temporal crescent in the phenomenon of blind-sight (*see also* Weiskrantz, 1972).

Perenin and Jeannerod (1978) have recently studied reaching to brief visual stimuli in patients who had undergone hemidecortication (hemispherectomy). The whole neocortex and hippocampus and part or all of the caudate nucleus were removed during this operation. No striate cortex therefore remained. In these patients a significant correlation was found between the position of bright targets within the hemianopic field and the position of corresponding hand pointings. Perenin and Jeannerod (1978) pointed out that, whether or not their subjects were *aware* of the stimulus within their blind hemifield, in order to give a response they had to guess in a forced-choice situation; the appearance of the stimulus was always preceded by an auditory signal. These observations, taken together, imply that the ability to reach for objects in the test situation reflects brain-stem mechanisms, the geniculocalcarine pathway having been destroyed.

Schneider (1969) in a review of the role of tectal and cortical pathways in visual function suggested that two visual systems exist in mammals and probably also in other vertebrates (*see also* Ingle, 1967; Schneider, 1967; Trevarthen, 1968). One mechanism, dependent on the superior colliculi and their connections, subserves the ability to orientate towards an object ('where is it?') and the other, represented by the geniculostriate pathway is concerned with the identification of the object ('what is it?'). Trevarthen (1968) used the broader concepts of *ambient* and *focal* vision in discussing these two systems, laying stress on the relation of motor responses to visual stimuli as a form of interpretation of visuo-motor activity in terms of body orientation and reaching in the former case, and of manipulation of objects in the latter. Schneider (1967; 1969), Trevarthen (1962; 1968) and later reviewers (*see* Weiskrantz, 1972; Weiskrantz *et al.*, 1977; Perenin and Jeannerod, 1978) have clearly indicated that these two functional systems are neither mutually exclusive nor anatomically discrete, but represent concepts of the organization of visuomotor function in personal and extrapersonal space.

The temporal crescent, dependent on nasal retinal cells with particular sensitivity for moving stimuli, is important for visual orientating responses, particularly for generating saccadic fixation responses but probably also in initiating rapid body or arm movements in response to sudden movements in the periphery. It can thus be regarded as having a particular role in ambient vision. Trevarthen (1968) pointed out that each monocular temporal field is in range for movements of the ipsilateral hand only, and that the monocular peripheral, and binocular central parts of the visual field are organized in a complementary way. The monocular peripheral field, acting as an event detector, is used to orientate the eyes and limbs so as to bring the object of regard within the view of the central and foveal fields for closer visual examination and for manipulation by the hands and mouth. The visual fields and motor system thus interact in an analogous way to the interaction of the posterior columns and motor system in voluntary movement (Denny-Brown, 1966). In man the tectal visual system seems to play a subservient role to the geniculostriate system, but the role of the temporal crescent in visual perception and visually guided behaviour, both at striate and tectal levels, has been relatively neglected. Our patients' residual visual abilities illustrate this in relation to striate lesions. It would be interesting to examine visual functions in the binocular central field and in the monocular temporal field, particularly in relation to visuomotor tasks in patients with tectal lesions.

SUMMARY

Four patients with hemianopias due to occipital infarction are described. In each of these patients there was useful residual vision in the unpaired temporal crescent. Moving stimuli were particularly well perceived in this part of the field. Preservation of the temporal crescent results in strikingly incongruous fields. The significance of this part of the visual field is discussed in relation to perception of movement and to the fixation reflex, and also with regard to recent reports of residual visual ability in patients with striate cortex lesions, and to the possible role of the monocular temporal field in striate and tectal visual systems.

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WORD-FORM DYSLEXIA

by ELIZABETH K. WARRINGTON *and* TIM SHALLICE[1]

(*From the National Hospital, Queen Square, London WC1*)

INTRODUCTION

'SPELLING dyslexia' is a phenomenon known to neurologists both as a variety of acquired dyslexia and as a component element of the syndrome of simultanagnosia. Patients are described as being able to read only 'letter-by-letter', so that the whole word is reconstructed from the (auditory) *names* of the letters, presumably relying on their intact spelling skills: literally C A T spells 'cat'. Reading becomes very slow and laborious and attempts to read more quickly are vitiated by numerous paralexic errors (Wolpert, 1924; Kinsbourne and Warrington, 1962). To encompass the co-occurrence of spelling dyslexia and the impairment of the perception of complex scenes Wolpert introduced the concept of simultanagnosia—the failure to apprehend the whole though the parts are well recognized. He clearly regarded these deficits as being at the level of comprehension; in the case of complex scenes, individual features could be identified but not the significance of the whole picture; similarly in the case of words, individual letters could be identified but not the whole word. Clinical and autopsy evidence suggests that simultanagnosia occurs in association with damage to the occipito-temporal region of the left hemisphere (Kinsbourne and Warrington, 1962, 1963).

Kinsbourne and Warrington (1962) investigated the capacity for simultaneous form perception in 4 patients with simultanagnosia. The striking feature in all 4 patients was that only one of two forms (letters, numbers, shapes) presented tachistoscopically could be identified. Insofar as a marked reduction in visual span of apprehension had been demonstrated for forms not comprising parts of a whole, they argued that it was more appropriate to view simultanagnosia as a limitation in perceptual processing rather than a failure to interpret complex percepts at the level of meaning as had been suggested by Wolpert. The demonstration of limited simultaneous form perception seemed sufficient to account for these patients' impairment of reading and of picture interpretation. However, Kinsbourne and Warrington did not in fact directly compare the perception of random items and items which were also parts of a whole, for example, random letter strings as compared with letters of a word. A further study of visual span of apprehension based on group data (Warrington and Rabin, 1971) confirmed the association of limited simultaneous form perception with posterior lesions of the left hemisphere, but the authors argued that it was more appropriate to implicate visual short-term memory than simultaneous perception as the basis of simultanagnosia. However, many of the patients in the group study were as impaired on the visual span tasks as the 4 cases of simultanagnosia reported previously, yet not one patient in the group study was noted to have a clinically obvious 'spelling dyslexia'. It therefore seems unlikely that a reduced visual span of apprehension (whether due either to a perceptual or to a short-term memory deficit) can account for the characteristic features of 'spelling dyslexia' namely letter-by-letter reading.

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[1] Present address: MRC Applied Psychology Unit, Chaucer Road, Cambridge.

In this study we report investigations of 'spelling dyslexia' in 2 patients with left posterior cerebral lesions. Neither patient was able to read with a semblance of normal speed and efficiency, both adopting a letter-by-letter strategy. Our investigations show that visual and perceptual factors including visual span of apprehension cannot account for letter-by-letter reading in these patients. The phenomenon of letter-by-letter reading is recorded quantitatively and certain predictions which follow are tested. We consider the status of simultanagnosia as a clinical entity and we postulate that the processes through which a visual *word-form* is attained are damaged in these patients.

CASE REPORTS

Case 1

R.A.V. (date of birth 1919) a right-handed university graduate in physics, and the deputy headmaster of a comprehensive school, had an intracranial hæmorrhage in April 1971, losing consciousness a few seconds after the onset of a severe headache. A left temporo-parietal intracranial hæmatoma was evacuated (*see* fig. 1) and five weeks after surgical intervention he regained consciousness. At that time he had a complete right homonymous hemianopia which has persisted unchanged. There were no other neurological signs except for a dysarthria; motor and sensory

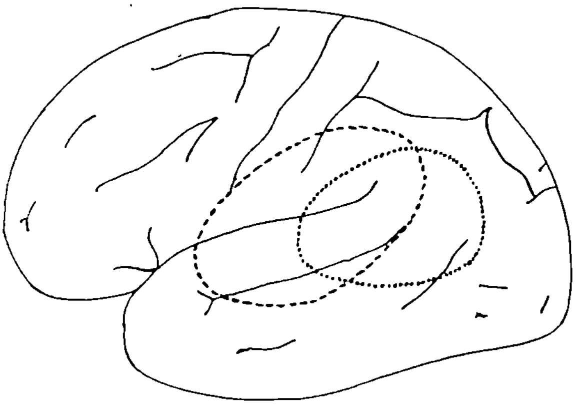

FIG. 1. Schematic diagram of location of lesions. R.A.V. ....; J.D.C. --------.

functions were normal. He was observed to be totally unable to read or write and he had dysphasia which affected, in particular, nominal functions. His language functions gradually improved and in October 1976, he was referred to the Psychology Department of the National Hospital for assessment of his residual reading difficulties. At this time his only complaint was of being able to read only very slowly and haltingly and of being unable to see words, especially long words, as a whole. After the initial test interview he volunteered to co-operate in the further investigation of his reading difficulty and he attended the National Hospital for eight two-hour sessions between November 1976 and August 1977. After this date there was a rapid and considerable improvement in his reading skills.

Psychological test findings. R.A.V. was tested on the WAIS and obtained a verbal IQ of 125 and a performance IQ of 118. On both the Picture Arrangement and the Picture Completion subtests of the WAIS (the test stimuli are complex visual scenes) he obtained an age-scaled score of 13 which is within the high average range. On the Peabody Picture Vocabulary test (which demands interpretation of complex pictorial material) he scored 142/150. His spontaneous speech was fluent and accurate and he used a wide vocabulary with facility. On a test of object-naming there was a very definite nominal dysphasia (10/15 correct); he did rather better in naming words from their description (12 correct) and on a test of verbal comprehension he scored at an average level (14/15 correct). (For further details of these tests see Coughlan and Warrington, 1978). His perceptual skills appeared entirely normal; for example, he scored 20/20 on a test of identifying objects photographed from unconventional views (Warrington and Taylor, 1973). There was no evidence of colour agnosia. On a dichotic listening task he showed a right ear superiority of 17 per cent.

On the Schonell graded word reading test he scored at a high level, his performance being virtually error-free (98/100), on the Nelson reading test (Nelson and O'Connell, 1978) he obtained a reading IQ of 121 (42/50); his spelling was also entirely satisfactory. However, qualitatively his reading was markedly abnormal. He was observed to spell out most words letter-by-letter, either aloud or under his breath and then reconstruct the word (correctly) from the auditory letter information. For example, he took thirty seconds to read the first 15 words of a prose passage. Very short words appeared to be read relatively normally but even these were read somewhat slowly. He had even more difficulty in attempting to read words written in script and he complained bitterly of the sheer length of time it took him to read an examination script. He was able to read non-words almost as efficiently as words. His mean time to read lists of 5 words and non-words (the stimuli in both lists were 4 and 6 letters) was 13.3 seconds and 14.0 seconds, respectively, and only very occasional errors were made. Numbers written in numerical form (for example, 1,340,210) were read quickly and efficiently. He thus appeared to have no difficulty in reading the constituent letters of the word but whole word reading was far from normal.

Case 2

J.D.C. a 35-year-old housewife, had left school at 15 without taking any leaving examinations. She was admitted to the National Hospital in September 1976 for investigation of intermittent 'blackouts' over the previous five years. On examination there was a very mild right hemiparesis and a homonymous upper right quadrantic defect. She had a mild nominal dysphasia and considerable difficulty in reading. There were no other neurological signs. EMI scan showed a large low density mass in the left temporo-parietal region (*see* fig. 1) and angiography indicated a large mass in the left temporal lobe which extended medially and posteriorly into the thalamus. A craniotomy was performed and a glioma (astrocytoma grade III) situated in the left temporo-parietal region was partially removed. Post-operatively her neurological status was essentially unchanged except that her nominal dysphasia was more pronounced.

Psychological test findings. J.D.C. was tested on the WAIS ten days pre-operatively and obtained a verbal IQ of 79 and a performance IQ of 76. On the Picture Completion and Picture Arrangement subtests of the WAIS she obtained age-scaled scores of 6 and 5, respectively, which are consistent with her scores on the verbal and spatial subtests. She scored 97/150 on the Peabody Picture Vocabulary test equivalent to an IQ of 88 which is the best available estimate of her premorbid level. (It should be noted that this test demands interpretation of complex pictorial material). Her spontaneous speech was fluent and for the most part accurate although some hesitancy and circumlocutory phraseology was apparent. She had a moderately severe nominal dysphasia which was unchanged post-operatively (post-operatively she scored 7/26 correct on the Oldfield naming test). Her perceptual skills appeared unimpaired, for example on the 'unconventional views' test she scored 19/20. Her verbal memory was severely impaired; she scored only 25/50 (chance level) on a two-choice recognition memory test for words. On a comparable visual memory test she scored 43/50 which is within the average range (E. K. Warrington, unpublished).

J.D.C. was able to spell and write. She scored 66 on the Schonell spelling test (Form A) which is fairly satisfactory for her relatively poor educational achievements. Her ability to identify words spelt to her was at a comparable level; she scored 47/60 on the first 3 columns of the Schonell graded word list (Form B).

Her reading skills were markedly impaired. On the Nelson reading test she scored only 3/50 (Nelson Reading IQ 89, Nelson and O'Connell, 1978). The Schonell reading test was not formally administered but she was observed to read even the shortest word letter-by-letter; she read the constituent letters of a word aloud reconstructing the word from the auditory letter information. She was unable to read script. Her reading rate was extremely slow and laborious and she was reluctant to persist in reading tasks; for example she read the first 11 words of a prose passage accurately but took 1′ 23″ to do so. Post-operatively, her reading skills appeared to be essentially unchanged.

She was tested in the Psychology Department pre-operatively for 3 sessions of approximately one and one-half hours. It was only possible to test her on two further occasions one and two weeks post-operatively.

EXPERIMENTAL INVESTIGATION

Peripheral Visual Factors

Experiment 1. Angle of attention scan. R.A.V.'s main symptom and complaint is that he is unable to read the word as a whole unit and must therefore read words letter-by-letter. It is well known that by no means all patients with a right homonymous hemianopia are dyslexic. Nevertheless it could be the case that in some patients there is a restriction in the visual angle (within the intact field) that can be effectively scanned or attended to in a brief or single exposure. Two tasks were devised to provide some measure of the attention span within a half field.

First, two upper case letters positioned so that there was a 'gap' of 3, 4, 5, 6 or 7 cm (1 cm subtends a visual angle of 1.4 deg) between them were presented tachistoscopically for 150 ms (e.g. X--------G). The Cambridge Tachistoscope (Model CT2) was used for this and all subsequent tachistoscopic experiments. The letters (upper case, Letraset No. 520, pt 28) were printed either side of the centre of the tachistoscope field but no fixation point was provided. After several practice trials R.A.V. was simply asked to report both letters. Secondly, two numbers were placed at either end of 4, 5, 6, 7 and 8 letter words (numbers and lower case, Letraset No. 520, pt 28, each letter subtended a visual angle of approximately 0.7 deg) and positioned in the centre of the tachistoscopic field (no fixation point); they were presented tachistoscopically for 150 ms. R.A.V. was asked to report both numbers. For both types of stimulus the gap sizes and the word length were tested in a fixed order from short to long. There were 5 stimulus cards for each condition.

The number of letters and number of numbers correctly reported for each condition is given in Table 1. Apart from a very few errors at the beginning of each task R.A.V.'s performance was good (J.D.C. did not attempt this task). It would seem that his angle of scan under these conditions of testing is in the order of 9 deg.

TABLE 1. ANGLE OF ATTENTION SCAN

Distance apart (cm)	3	4	5	6	7
Letters correct	9/10	10/10	9/10	10/10	7/10
Distance apart (letters)	4	5	6	7	8
Numbers correct	8/10	8/10	9/10	10/10	10/10

Experiment 2. Selective attention. When reading letter-by-letter at his own speed R.A.V. attains a satisfactory reading level. It is possible that letter-by-letter reading is merely a strategy adopted by an intelligent man to overcome a possible impairment of selective attention.

Performance on reading single isolated letters was compared with performance on reading of letters in an array or letters flanked by letters printed in a different colour, two tasks shown to be markedly impaired in two patients in whom we have argued there was a failure of selective attention (*see* Shallice and Warrington, 1977). The array consisted of 5 rows of 5 letters, typed with single spacing. A red upper case letter was 'flanked' by 4 (2 each side) upper case black letters typewritten with normal spacing (e.g. XRMLY). The arrays task was unpaced and a rate of 1 per two seconds was used for the flanking experiment. The number of letters correctly read singly, in an array and flanked, for each patient, is given in Table 2. R.A.V. had no difficulty on these two tasks and J.D.C. was only minimally impaired.

TABLE 2. VISUAL SELECTIVE ATTENTION

	R.A.V.	*J.D.C.*
Singles	25/25	25/25
Array	25/25	22/25
Singles	24/24	24/24
Flanked	24/24	22/24

Number of letters correctly reported for each condition of presentation.

Experiment 3. Visual short-term memory. In view of the previously reported association of letter-by-letter reading with a very reduced visual span of apprehension (*see above*) it was necessary to obtain some estimate of the visual short-term memory capacity of these patients.

Three tasks of visual short-term memory were attempted by R.A.V. (there are data for J.D.C. on only one of these).

(a) Three consonants were positioned either vertically (5 deg) to the left of a central fixation point, or horizontally in the visual field so that the edge of the right-hand letter was ½ deg from the fixation point (upper case Letraset No. 1447, pt 48). Twenty horizontal and 20 vertical stimulus cards were presented in alternating blocks of 10 using a 50 ms exposure duration. R.A.V. reported 55/60 of the horizontal letters and 57/60 of the vertical letters.

(b) Fifteen 5-letter strings of 0 order transitional probability (random letter strings) and 15 of 4th order probability (for further details *see* Warrington and Rabin, 1971) were presented tachistoscopically to R.A.V. for 100 ms and to J.D.C. for 50 ms positioned in a row so that the centre letter was in the centre of the field. A central fixation point was provided but subjects were not instructed to fixate it. R.A.V. reported 53 per cent of the 0 order letters and 72 per cent of the 4th order letters and J.D.C. reported 40 per cent of the 0 order letters and 43 per cent of the 4th order letters. These values are in reasonable accord with the level of performance obtained by a group of patients with left hemisphere lesions tested under similar but not identical conditions, 50 and 77 per cent, respectively (Warrington and Rabin, 1971).

(c) Four quasi-random numbers (all different) were printed (Letraset No. 1276, pt 42) in a quartered square, e.g.

6	4
3	9

which was positioned in the centre of the tachistoscopic field. There were 20 stimulus cards and a 100 ms exposure duration was used. R.A.V. reported 75/80 of the numbers correctly. Using a similar but not identical procedure, a group of patients with lesions of the left hemisphere without a spelling dyslexia were able to report 55 per cent of strings of 5 digits (Warrington and Rabin, 1971).

Comment

In this group of experiments we have attempted to assess to what extent visual and perceptual factors can account for the reading difficulties experienced by these two patients. A visual field defect cannot be critical because we have observed patients with complete right homonymous hemianopia who are able to read quite normally; conversely, letter-by-letter reading has been observed in patients with full visual fields (Kinsbourne and Warrington, 1963; Vincent, Sadowsky and Reeves, 1977). In addition there was no evidence for any specific impairment involving selective attention in either patient or angle of attention scan in R.A.V. This latter finding also effectively eliminates visual neglect as a contributory factor to his reading difficulties. In addition, R.A.V.'s visual span of apprehension for letters and numbers, though weaker than normal, was comparable with the group of patients with lesions of the left hemisphere studied by Warrington and Rabin (1971). J.D.C. scored at a somewhat lower level, but even so, her performance on visual span of apprehension tasks was considerably superior to those patients reported previously, who had a reliable span of only 1 (*see* Kinsbourne and Warrington, 1962). We would infer from these observations that the perception of the constituent parts of a word is reasonably normal.

Letter-by-Letter Reading

Experiment 4. Reading speed and the effect of word length. The previous three experiments attempt to eliminate visual and perceptual factors including visual short-term memory as the basis of 'spelling dyslexia'. Our aim in this experiment is to establish that R.A.V. and J.D.C. were indeed reading letter-by-letter by demonstrating not only that their speed of reading words is exceptionally slow but that their reading speed is directly related to word length.

R.A.V. read sets of 10 high frequency words typed in a column on a quarto page. He read 8 sets of 4-letter words and 8 sets of 6-letter words presented in an ABBA design. Four sets of each word length were typed in lower case and 4 were *typed* in mixed upper and lower case (that is, lower and upper case letters not equated for size). This experiment was repeated after a gap of eighteen months. The mean total time (recorded by stop watch) to read each type of 10-word list is given in Table 3. On each occasion there were significant effects of both length (I $F(1, 12) = 24.0 P < 0.01$; II $F(1, 12) = 21.7$ $P < 0.01$) and case (I $F(1, 12) = 10.08$ $P < 0.01$; II $F(1, 12) = 11.1$ $P < 0.01$). Neither interaction term was significant. J.D.C. read 8 sets of five 4-letter words, 4 sets were typed in lower case and 4 sets were typed in mixed case. The mean total time to read each type of 5-word list is given in Table 3. There were occasional errors in J.D.C.'s reading. R.A.V.'s reading was entirely accurate on the first occasion, and on the second occasion he made 7 errors on the mixed case words.

The speed of reading is clearly very slow indeed for both patients. The normal reader takes up to five seconds to read a set of the 10 lower case words attempted by R.A.V. (personal observation). There is a striking word length effect in R.A.V. which cannot in fact be detected on this task in the normal reader.

TABLE 3. SPEED OF READING AND WORD LENGTH

	R.A.V. I		*R.A.V. II*		*J.D.C.*
Word length	4	6	4	6	4
Lower case	19.0	29.0	13.6	23.1	32.0
Mixed case	25.0	39.7	20.5	29.5	34.7

Time in seconds to read columns of words (R.A.V. 10 words, J.D.C. 5 words).

Experiment 5. Reading script. Our aim in this and in the following experiment was to use techniques which on the one hand minimize the possibility of letter-by-letter reading, and at the same time maximize the necessity for whole word reading. Reading script, as compared with print, would appear to meet this requirement. The individual letters can be almost indecipherable so that they can only be identified in conjunction with the adjoining letters. For the present experiment we have used the clearest Letraset script available and even so it can be seen in fig. 2 that by masking the adjoining letters the constituent letters become ambiguous.

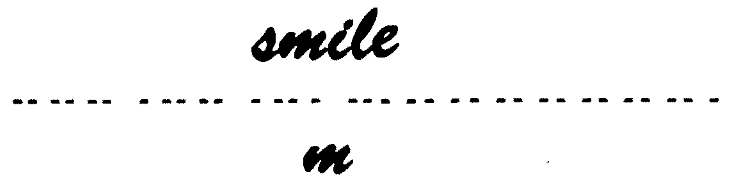

FIG. 2. Example of script used—whole word and single letter from it.

Three, five and seven letter high-frequency words were arranged in columns of 3 words printed in lower case print or in lower case script (2 matched sets) (Letraset No. 520, pt 28 or No. 279, pt 36). R.A.V.'s mean time to read each type of set is given in Table 4. There are significant effects of both script and word length (F (1, 18) = 11.8 $P < 0.01$ and F (2, 18) = 7.6 $P < 0.01$ respectively). No errors were made when reading print and only 4 errors were made with script. J.D.C. only attempted 3-letter words, reading 10 sets of printed words and 10 sets of script words. Her over-all level of performance was poor and therefore an error score rather than speed of reading was recorded (*see* Table 4). She made significantly more errors with script than with print ($\chi^2 = 5.62$, $P < 0.02$ (1 d.f.)). It is clear that this script, in spite of being relatively clear and presenting no difficulty to the normal reader, is very much more difficult for both R.A.V. and J.D.C. to read than is print.

TABLE 4. SCRIPT READING AND WORD LENGTH

	R.A.V.			*J.D.C.*
Word length	3	5	7	3
Print	5.5	8.6	9.0	23/30 (correct)
Script	7.9	12.1	14.0	13/30 (correct)

Time in seconds to read columns of 3 words (R.A.V.) and number of words correctly read (J.D.C.).

Experiment 6. Tachistoscopic reading. Tachistoscopic presentation would also appear to maximize the need for whole word reading at least for words which exceed the visual span of apprehension.

J.D.C.'s tachistoscopic word reading was tested using a pool of 24 high frequency 3-letter words, 24 high frequency 6-letter words and 24 pronounceable 3-letter nonsense words (lower case Letraset No. 520, pt 28). The exposure duration was 200 ms and she was tested in blocks of eight according to a Latin Square design. The number of words and the number of letters correctly reported are given in Table 5. Her over-all level of performance was extremely poor, and in addition, there appeared to be little gain in reading words as compared with nonsense words.

Our attempts to assess R.A.V.'s tachistoscopic reading skills were not entirely satisfactory. His relatively good visual span of apprehension necessitated using words which exceeded his visual span of apprehension, but then these longer words fell partially in his peripheral visual field (he had a macular splitting right homonymous hemianopia). Nevertheless the following observations were recorded. Fifty concrete words well within his reading vocabulary (*see* Case Report) but less than A (occurrence less than 50 words per million) in Thorndike-Lorge frequency (Thorndike and Lorge, 1944), for example, antler, falcon, steeple (chosen to be appropriate to the Peabody picture vocabulary stimuli) ranging in length from 6 to 8 letters and printed in lower case (Letraset No. 520, pt 28) were presented tachistoscopically using a 500 ms exposure duration. He reported only 42 of

TABLE 5. TACHISTOSCOPIC READING

	Words correct	*Letters correct*
6-letter words	0	56
3-letter words	12	57
3-letter nonsense syllables	9	52

Number of words (maximum 24) and letters (maximum 144, 72) correct (J.D.C.).

these words correctly. On those occasions he failed to read the word aloud, he immediately attempted to match its meaning with one of a set of 4 pictures. He selected the correct picture for only 3/8 words. On a similar task in which 50 4- to 7-letter words (the most concrete) from the English Picture Vocabulary test, written in script (Letraset No. 279, pt 48) were presented tachistoscopically using a 500 ms exposure duration, he read 41/50 correctly. Of the 9 words he failed to read, he scored 1/9 correct on the picture choice task. Two patients with a macular splitting right homonymous hemianopia but normal reading due to left occipital infarctions were tested as controls. Neither patient made any errors under these conditions.

Tachistoscopic presentation was also used to assess whether the concrete/abstract dimension affected R.A.V.'s reading skills. A pool of 72 words (4, 6 and 8 letters) matched for frequency, half of which were concrete and half of which were abstract (Brown and Ure (1969) C > 4.7 and C < 4.7, respectively) were presented using a 100 ms exposure duration. He reported correctly 30/36 of the abstract words and 28/36 of the concrete words. Thus his performance on this task is generally weak and there was no suggestion of a significant abstract/concrete effect.

DISCUSSION

It has been shown that whole word reading was not possible for our two patients and that they do in fact resort to reading letter-by-letter. Their speed of reading is exceptionally slow and furthermore it was shown that the time to read unrelated words is strongly related to the total number of letters. Two techniques were used to maximize the necessity for whole word reading by preventing the subject resorting to the strategy of letter-by-letter reading, namely, script reading and tachistoscopic presentation. Script was strikingly more difficult than print for both patients. For J.D.C., who was less able to use intelligent guessing, more errors were recorded, for R.A.V. reading script was qualitatively similar to reading print but much slower. For both R.A.V. and J.D.C. the reading of whole words presented tachistoscopically was markedly impaired.

We would argue that the capacity for whole word reading in our two patients was either absent or so impaired as to vitiate 'normal' reading. It then becomes relevant to consider the locus of this deficit. We have rejected the possibility that letter-by-letter reading can be attributed to visual or perceptual deficits. Three further possibilities seem to be candidates for the functional basis of the phenomenon of letter-by-letter reading—a deficit in the comprehension of the written word, a failure in the transmission of information from the right to the left hemisphere and impairment of a visual word-form system.

Wolpert (1924), in originally describing simultanagnosia, put forward the first of these interpretations. He held that the capacity for reading letter-by-letter was retained through the preservation of comprehension of individual letters, but that the comprehension of 'wholes' including whole words was damaged. This seems unlikely to be the explanation of letter-by-letter reading for a number of reasons. First, the status of simultanagnosia as a syndrome must be questioned. Complex picture interpretation was relatively unaffected in both these patients; indeed R.A.V. scored at an above average level on a number of tests of picture interpretation, including Picture Arrangement and the Peabody picture vocabulary test, so the two components of the syndrome can be selectively impaired. Thus Wolpert's over-all view of the syndrome cannot be entirely valid. Secondly, if the agnostic deficit in simultanagnosia were at the level of comprehension (an associative agnosia), spelling dyslexia would be within the domain of the 'central acquired dyslexias' (Shallice and Warrington, 1980). Effects of the concreteness of word stimuli, the existence of semantic errors (Marshall and Newcombe, 1973; Shallice and Warrington, 1975; Richardson, 1975) or by analogy with the work of Warrington (1975), the presence of partial comprehension of words which could not be read (*see* Warrington and Shallice, 1979) would then be expected. No such factors appeared to have any effect on the reading performance of these patients. More important, however, are the recent observations that 'phonological' reading is possible in the absence of written word comprehension, so-called surface dyslexia (Marshall and Newcombe, 1973) or semantic dyslexia (Shallice and Warrington, 1980). This syndrome is characterized by a disproportionate difficulty in the reading of irregular words (not noted with spelling dyslexia). Thus to account for letter-by-letter reading at the level of a comprehension deficit an additional deficit implicating phonological analysis would be necessary for the dyslexic difficulties to become apparent. This appeared not to be the case. R.A.V. could read nonsense syllables and nonsense words and in general the phonological processing of both patients seemed intact. They could write and spell at a level commensurate with their education. It therefore seems necessary to conclude that the letter-by-letter strategy is an attempt to compensate for damage to a stage in the reading process prior to phonological or semantic analysis.

A second possible explanation is that the letter-by-letter reading strategy arises from an inability to transmit graphemic information from the right to the left hemisphere in those patients with a right homonymous hemianopia. A disconnection explanation is, of course, the standard explanation of dyslexia without dysgraphia (*see* Dejerine, 1892; Benson and Geschwind, 1969) and some authors view spelling dyslexia as being within this over-all category (*see* Benson, Brown and Tomlinson, 1971; Greenblatt, 1973). Benson *et al.* (1971) specifically state that in their patients 'word blindness did not occur in the face of fully normal letter reading' so implying that word reading and letter reading deficits are on a continuum. Within such a disconnection framework letters are spared because they are less complex stimuli and so presumably a word imposes a greater information load on the damaged transmission pathways than a letter. Indeed, Staller, Buchanan, Singer, Lappin and Webb (1978) described a patient whose reading speed was also determined by word length and interpreted their findings in terms of this standard disconnection hypothesis. However, from Warrington and Rabin's (1971) findings it would appear that short-term storage of letter strings (which in 'information capacity' terms imposes a greater load than a word of the same length) primarily involves the posterior parts of the left hemisphere. Thus for patients with a right homonymous hemianopia, adequate span of apprehension performance must involve virtually as heavy an information load on the callosal transmission pathways as does word reading. The dissociation between letter span and word reading makes an explanation of spelling dyslexia in terms of the classical disconnection theory most implausible. It should, in any case, be pointed out that spelling dyslexia can occur with full fields and with a lesion site somewhat distant from the corpus callosum (Kinsbourne and Warrington, 1963; Vincent *et al.*, 1977).

By contrast the properties of the reading performance in the present two patients seem fully compatible with, and indeed could be predicted by, a deficit of a visual word-form unit. The concept of a word-form or equivalent unit is implicit in all theories of word reading which postulate that words are normally read as wholes. The first demonstration of 'whole word' reading was provided by Cattell (1886). More recently, these concepts of whole word reading have been incorporated into an information processing approach, Allport (1977) postulating a whole-word pattern analyser and Morton (1979) a visual logogen, both considered to be essential stages in the operation of the 'direct route' to meaning. We concur, but in our view the word-form must also be attained prior to phonological analysis in addition to being prior to semantic analysis (*see* fig. 3).

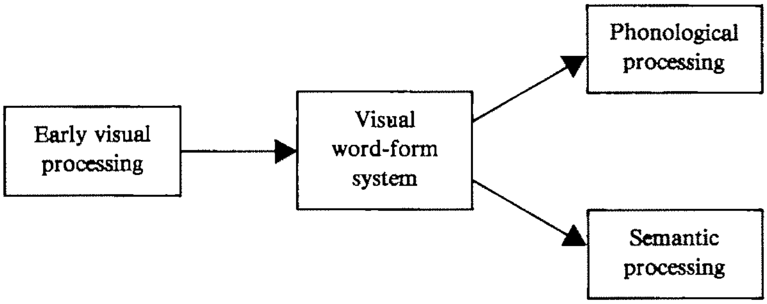

FIG. 3. Schematic model of the relationship between the word-form system and other stages in the reading process.

We do not wish to equate the concept of a word-form with that of an ideogram, implicit in many early theories of reading, and indeed, in a different context it has already been shown that in 'direct' route reading words are not mere ideograms (Saffran and Marin, 1977). We would define a visual word-form system as follows: that which parses (multiply and in parallel) letter strings into ordered familiar units and categorizes these units visually. The components can range in size from graphemes, syllables, morphemes to whole words. Thus, reading by the 'direct' route obviously uses only the larger type of word-form units but the other types of unit are likely to be implicated in addition in reading by the phonological route. It should be noted that this formulation of a word-form unit allows more flexibility than does the notion of an ideogram. (For a full discussion of the necessity for this elaboration of the concept of the word-form *see* Shallice and Warrington, 1980). In the context of letter-by-letter reading the very pronounced effect of mixed case for

R.A.V. may seem paradoxical (Experiment 4). However, in our view any contribution of the word-form system to R.A.V.'s reading performance would be expected to be disrupted by an alteration to the word-form which would impose only a small additional processing difficulty for the normal reader (Smith, 1969; Coltheart and Freeman, 1974). This assumption that the word-form system exists as a distinct stage of the reading process is clearly strengthened by the identification of its selective impairment on a structural basis. This, we have argued, occurs in patients with letter-by-letter reading.

It is worth considering this word-form dyslexic syndrome in relation to assertions regarding the residual reading skills of the right hemisphere (for example, preservation of the reading of concrete nouns (Marcel and Patterson, 1978)). R.A.V.'s performance on word/picture matching described in Experiment 6 was surprisingly poor, especially as he made full use of highly intelligent guessing strategies based on correct recall of the first few letters from his visual short-term store. These error responses must reflect not only a failure to read aloud but also a failure to comprehend the written word. Similarly he failed to show any differential preservation of the reading of concrete words which one would predict from his view of 'right hemisphere' reading. At least in the case of R.A.V. it would appear that the residual reading of the undamaged right hemisphere is most unimpressive. Moreover, many patients with letter-by-letter reading reported previously had sustained unilateral damage to the left cerebral hemisphere, as did the two patients reported in this study. If our interpretation of the syndrome is correct, it follows that a relatively early stage of the reading process is lateralized to the left hemisphere. This makes it implausible that the normal right hemisphere would have much capacity for comprehending the written word.

SUMMARY

In this study we have reported our investigations of two patients with an acquired dyslexia characterized by letter-by-letter reading, whole word reading being apparently impossible. It has been shown that this phenomenon of letter-by-letter reading cannot be accounted for by visual or perceptual factors nor by impairment of visual span of apprehension. The exceptionally slow speed of reading was documented and a clear relationship between word length and reading speed established. Performance on tasks considered to maximize whole word reading which at the same time prevent the possibility of letter-by-letter reading, namely, reading script and reading with tachistoscopic presentation, was impaired. The satisfactory performance of these two patients on tasks of picture interpretation suggests that the two components of the syndrome simultanagnosia, letter-by-letter reading and piecemeal perception of complex scenes, are dissociable. Three alternative explanations of letter-by-letter reading are considered and we conclude that in this type of acquired dyslexia there is damage to the system through which a visual word-form is attained.

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DISORDERED INHIBITION IN INTERNUCLEAR OPHTHALMOPLEGIA

ANALYSIS OF EYE MOVEMENT RECORDINGS WITH COMPUTER SIMULATIONS

by STEVEN E. FELDON, WILLIAM F. HOYT *and* LAWRENCE STARK

(*From the Neuro-ophthalmology Unit, Departments of Neurology, Neurosurgery and Ophthalmology, University of California, San Francisco Medical Center, San Francisco 94143, USA*)

INTRODUCTION

INTERNUCLEAR ophthalmoplegia is characterized clinically by weakness of the adducting eye and dissociated nystagmus of the abducting eye. The paresis of the adducting eye can either be total (Smith and Cogan, 1959) or partial (Smith and David, 1964). Electro-oculographic studies have documented these abnormalities and permitted detection of subclinical cases (Nelson and Engrav, 1969; Kommerell, 1971; Solingen, Baloh, Myers and Ellison, 1977). Recently, more extensive oculographic analyses have been reported which have quantitated the oculomotor abnormalities (Fricker and Sanders, 1975; Bird and Leech, 1976) and related the deficits in internuclear ophthalmoplegia to current control theory (Pola and Robinson, 1976; Kirkham and Katsarkas, 1977; Baloh, Yee and Honrubia, 1978). The application of control theory to oculomotor disorders is especially relevant because eye movements faithfully follow their neural controller signals.

Normally, the pattern of neural activity for saccadic (i.e., rapid) eye movements consists of a pulse-envelope of high frequency discharge to the agonist, followed by a step-envelope of higher tonic firing sufficient to hold the eye at the new position. The antagonist is completely inhibited during the pulse of agonist activity, after which it receives a lower step of tonic neural input.

These pulse-steps of innervation to the eye muscles occur as frequently as every 150 to 200 ms as predicted by the sample-data theory (Young and Stark, 1963) and occasionally can occur even more closely spaced (Bahill and Stark, 1975). The amount of innervation (pulse height times duration) determines the amplitude of the phasic component of the saccade. Using experimental data and computer simulations, Bahill, Clark and Stark (1975) derived a 'main sequence' curve which related saccadic amplitude to duration, peak velocity and peak acceleration. These relationships provide criteria by which to compare normal saccades with those made by patients with oculomotor dysfunction. Saccadic movements that do not have durations, velocities, and accelerations which lie on the 'main sequence' curve represent alterations of the pulse-step of reciprocal innervation to the eye plant.

In the present study, high resolution infra-red recording techniques are employed in order to evaluate quantitatively fine details of saccadic trajectories in internuclear ophthalmoplegia. Using an adaptation of the Cook-Stark reciprocal innervation model for eye movements (1967), we investigate the control signals necessary to simulate both abducting and adducting eye movements. Particular attention is directed towards the role of deficient inhibition of the medial rectus, known to be present from electromyographic studies (Loeffler, Hoyt and Slatt, 1966; Gonzalez and Reuben, 1967; Huber and Esslen, 1972).

METHODS

Selection of Patients

Eye movements of 17 patients seen by the Neuro-ophthalmology Unit of the University of California, San Francisco Medical Center with clinical signs suggesting internuclear ophthalmoplegia were recorded between 1974 and 1978 (Table 1).

TABLE 1. CASES OF INTERNUCLEAR OPHTHALMOPLEGIA

Case (No.-age-sex)	*Diagnosis*	*INO symmetry*
1-47-F	Multiple sclerosis	Left = Right
2-45-M	Multiple sclerosis	Right > Left
3-15-M	Medulloblastoma	Left > Right
4-30-M	Multiple sclerosis	Left = Right
5-53-F	Multiple sclerosis	Left > Right
6-57-F	Multiple sclerosis	Right > Left
7-53-F	Multiple sclerosis	Left = Right
8-53-M	Multiple sclerosis	Left = Right
9-50-M	Multiple sclerosis	Left = Right
10-58-F	Brain-stem stroke	Left > Right
11-57-F	Brain-stem stroke	Left > Right
12-49-M	Multiple sclerosis	Left = Right
13-49-M	Multiple sclerosis	Left = Right
14-48-M	Multiple sclerosis	Right > Left
15-56-F	Multiple sclerosis	Right = Left
16-33-M	Midbrain glioma	Right = Left
17-41-M	Multiple sclerosis	Left > Right

INO = internuclear ophthalmoplegia.

Recording Technique

Eye movements were measured by photo-electric cells that detected infra-red light reflected from the sclera and iris. Cell pairs were mounted on spectacle frames and positioned at the limbus in the horizontal plane of each eye. The difference in signal strength between each pair of photocells was proportional to horizontal eye position (Stark, Vossius and Young, 1962). Eye position signals were calibrated and displayed on a six-channel curvilinear recorder. Left eye position was recorded above right eye position. Upward deflections corresponded to leftward eye movements and downward deflections to rightward eye movements. Position signals were also electronically differentiated to provide simultaneous velocity recordings. These were recorded, left eye over right eye, above eye position channels.

All stimulus and response data were simultaneously recorded on a seven-channel FM tape recorder at $7\frac{1}{2}$ ips. Subsequently, these data were recharted at a paper speed of 150 mm s^{-1} on an Elema Schönander Mingograf with an estimated high frequency cut-off of 1000 Hz. All measurements were made from carefully calibrated, ortholinear recordings. Some records were also analysed by digital methods and displayed using a PDP-8 minicomputer. Occasional patients were recorded by d.c. electro-oculography, but these records were not used in our quantitative analysis.

Protocol

Each patient was seated comfortably 1 m from a white, dimly lighted screen. Photocell spectacles were carefully positioned and the eyes were evenly illuminated by an infra-red light source. A 1 cm circular target of light subtending 0.57 degrees of visual angle was projected by a mirror galvanometer system. Patients were instructed to look at the target. In this manner, steady fixation, smooth pursuit, and saccadic jumps were elicited in the horizontal plane. Target jumps of 5 to 30 degrees in 5 degree steps were presented in order to produce saccades to primary position, away from primary position, and symmetrically and asymmetrically across primary position. For this study, only saccades to and away from primary position were used. Recalibration was performed every 2 to 3 min during each recording session. At least 150 saccadic responses were obtained from each patient.

Computer Simulation

Internuclear ophthalmoplegia was simulated by an adaptation of the Cook-Stark sixth order model of the human eye-positioning mechanism (Cook and Stark, 1967). The model takes into account all mechanical forces acting on the globe (fig. 1). Reciprocal innervation of the agonist and antagonist built into the original model was modified for the purpose of simulating internuclear ophthalmoplegia so that agonist and antagonist neural signals could be varied independently. Abducting and adducting saccadic pairs were simulated simultaneously.

Differential equations were integrated at 0.2 or 1 ms intervals in order to obtain the same high level of resolution as was achieved in the clinical recordings. Previous evaluations of saccades generated by this model (Hsu, Bahill and Stark, 1976; Lehman and Stark, 1979) have shown good correspondence to experimental and clinical eye movement data.

RESULTS AND ANALYSIS

Defective Saccadic Trajectories During Adduction. Phasic and Tonic Components

The oculographic appearance of adducting saccades varied considerably from saccade to saccade in each patient and also from patient to patient (fig. 2). The position trace showed either a smooth trajectory or a steep initial segment followed by a more gradual slope. Velocity traces, even for the 'smooth' trajectories, often demonstrated an initial rapid phasic component of measurable duration.

Amplitudes for the phasic components of adducting saccades varied from nondetectable to normal. Peak velocities of the phasic components varied, but were always subnormal. Durations of the phasic components, as measured from the velocity traces, were prolonged.

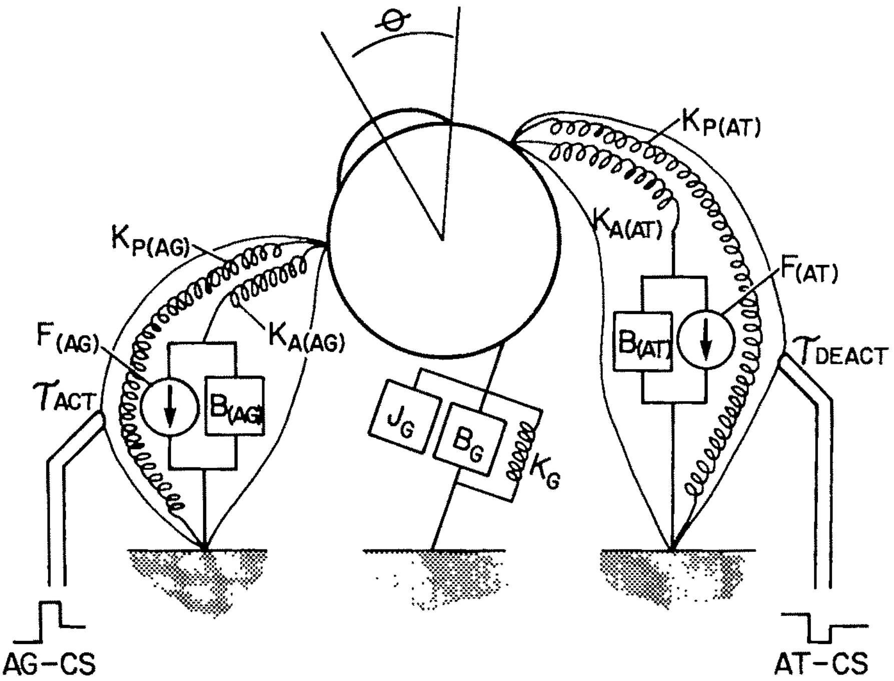

FIG. 1. Biochemical model of the eyeball plant. Agonist (*left*) and antagonist (*right*) muscles are each represented by series (K_A) and parallel (K_P) elasticities, as well as by viscosities (B). AG-CS and AT-CS are the reciprocal pulse-step controller signals for the agonist and antagonist, respectively. These controller signals act through time constants of activation (τ_{ACT}) and deactivation (τ_{DEACT}) to generate agonist (F_{AG}) and antagonist (F_{AT}) forces which result in eye movements.

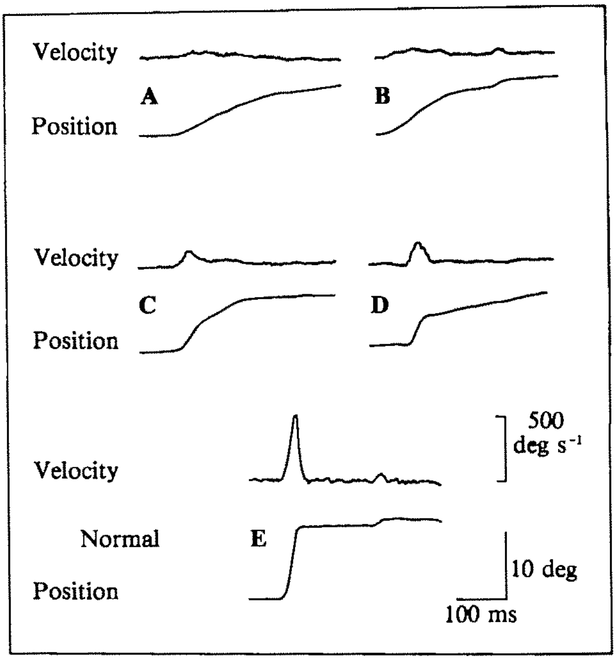

FIG. 2. Eye movement recordings from different patients with severe (A and B) or mild (C and D) deficiency of adduction. Phasic components which are difficult to distinguish in position records are more easily recognized in the derived velocity traces. An adducting movement from a normal subject (E) is provided for comparison. (In this and all subsequent figures showing actual or simulated eye movement recordings, leftward movements are upwards and rightward movements are downwards.)

The trajectories of tonic components of adducting saccades approached, but often did not reach the target's position. Their peak velocities were slow and fell below the normal amplitude-velocity relationship predicted by the main sequence for vergence-like movements.

Computer simulations of abnormal adducting saccades, which corresponded closely to the trajectories recorded in our patients, were achieved by varying pulse height in the model, while pulse duration and step level remained constant (fig. 3).

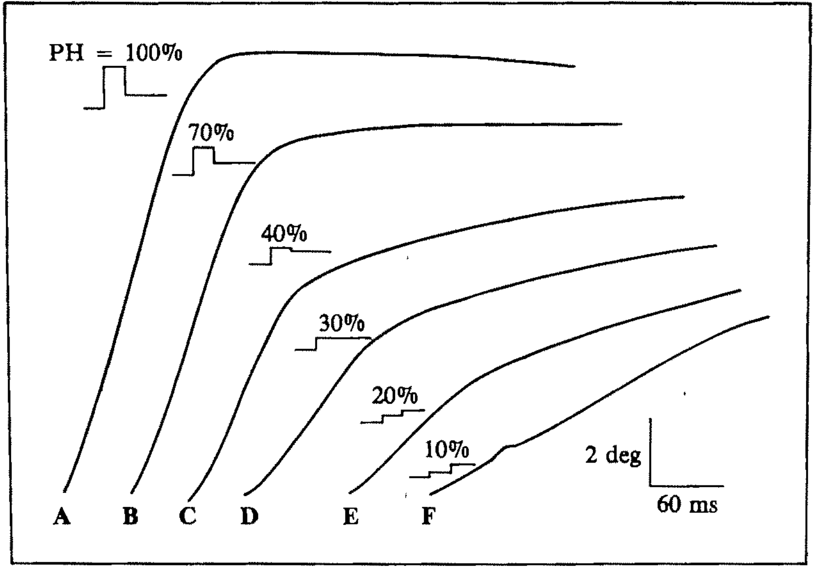

FIG. 3. Computer simulations of adducting saccades in internuclear ophthalmoplegia. Pulse-steps of agonist innervation are shown next to the position trace of each simulated saccade. Pulse width is kept constant while pulse height (PH) is varied from 10 to 100 per cent of normal. The assigned level of tonic innervation is held constant at 70 per cent of normal in each instance. Pulses are allowed to go below step levels for demonstration purposes. Whether pulses actually can be smaller than steps of innervation is unknown.

Defective Saccadic Trajectories during Abduction

Subtle irregularities in the trajectories of abducting saccades were almost constant findings on high resolution oculographic recordings from our patients. These were often more marked on the side with greater deficiency of adduction. Though sometimes difficult to detect in the position tracings, abnormalities of the phasic components of abducting saccades were obvious in the velocity tracings (fig. 4). Here, the usual single velocity peak of the phasic component was replaced by a more complicated, multi-peaked waveform. The durations of the abducting saccades were prolonged, and their peak velocities were often slower than predicted by the main sequence. Nevertheless, abducting saccades were close to normal in amplitude.

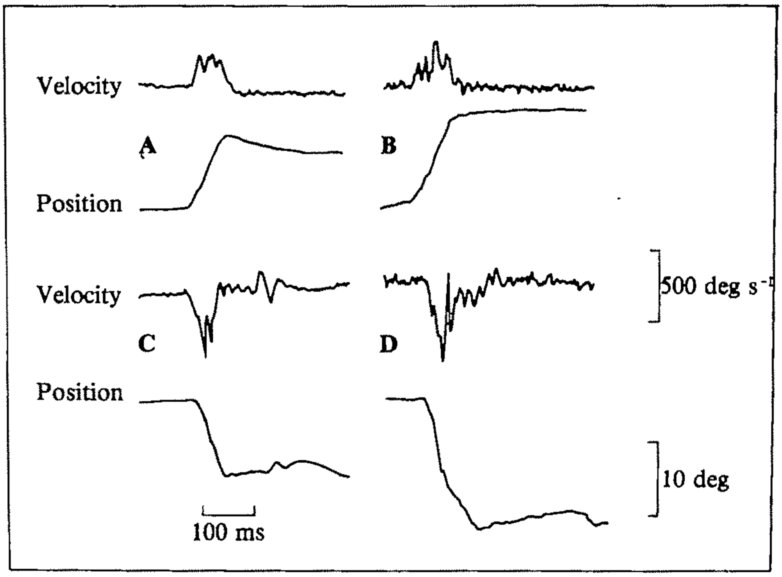

FIG. 4. Position and velocity traces of 'fractionated' abducting saccades in different patients with internuclear ophthalmoplegia. Changes in saccadic trajectories which are difficult to appreciate on position records are readily appreciated as multi-peaked velocity traces.

When subcomponents of these 'fractionated' abducting saccades were measured and their duration-amplitude and peak velocity-amplitude relationships determined (fig. 5), some points fell on the main sequence while others fell above or below (not shown).

Subcomponents with normal or slow peak velocities and with almost normal or prolonged durations could be produced by controller signals arising at the level of the pulse generator. However, those subcomponents with abnormally high peak velocities and short (10 to 11 ms) durations could not be produced by ordinary controller signals from the saccadic pulse generator. As determined by the main sequence, even the smallest of saccades have durations of greater than 20 ms (Bahill, Clark and Stark, 1975). The pulse signals for saccades greater than a few degrees cause firing of all motor neurons (Keller, 1974). Saccades with abnormally high velocities do not exist. Therefore, these high-velocity subcomponents are not independent saccades, but instead are the result of interrupted saccadic controller signals.

Assuming the integrity of the nuclear and infranuclear components of the oculomotor system, we would not expect the excitatory neural signals for abducting eye movements to be deficient in internuclear ophthalmoplegia. Instead, using computer modelling, we explored the possibility that intermittent neural pulses to the antagonist exercized a braking effect on abducting saccades and caused the observed fractionation. Such a model must account for the oculographic findings. In particular, saccades must be generated which simulate those

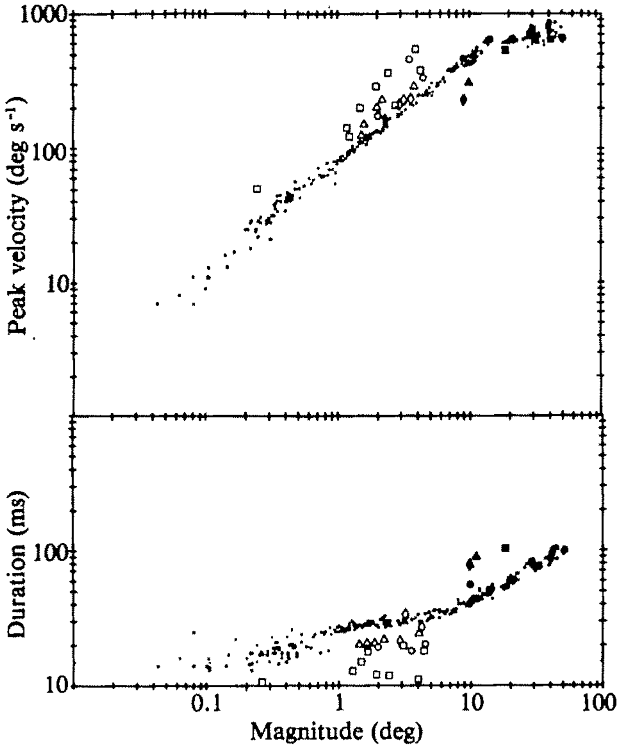

FIG. 5. Duration-amplitude and peak velocity-amplitude relationships for subcomponents of abducting saccades (*open symbols*) and for over-all saccades (*closed symbols*) shown in fig. 4, compared to normal subjects (Bahill and Stark, 1975). Subcomponents often have durations shorter than expected and peak velocities higher than expected for a given saccadic amplitude. Despite the abnormal trajectories, over-all saccadic velocities and durations may be close to normal. (4A = ◇, 4B = △, 4C = ○, 4D = □).

abnormal abducting saccades having only slightly prolonged duration, normal amplitude and peak velocity of the phasic component, and faster and shorter than expected subcomponents. When two brief (1 ms) braking bursts by the antagonist muscle were introduced into the model and their onset varied from 1 to 11 ms after the beginning of the agonist burst, the model produced saccades which fulfilled these requirements (fig. 6). By varying the onset and duration of braking bursts in the model, the amplitudes of the simulated saccades could be adjusted and the forms of the velocity curves changed to match all the variations seen in our patients' abducting saccades.

Comparison of Durations for Phasic Saccadic Components in the Adducting and Abducting Eyes

In recordings of binocular eye movements, durations of phasic saccadic components were prolonged, but equal in the two eyes (fig. 7). Exceptions were found when the adductor was so slow that the phasic component was unmeasurable or when the phasic component was of delayed onset.

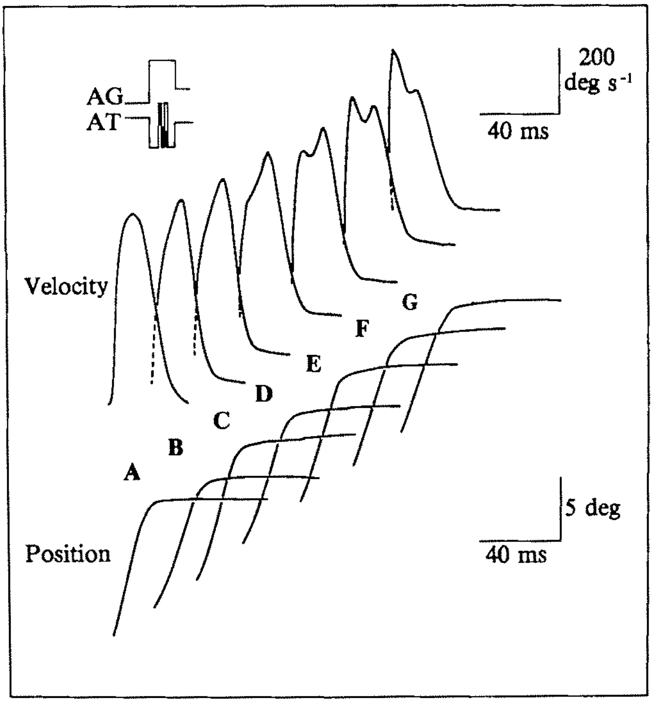

FIG. 6. Position and velocity traces of several computer-simulated abducting saccades with characteristics similar to patient recordings shown in fig. 4. The controller signals (*upper left*) which produce these saccadic trajectories require failure of inhibition in the medial rectus. In this series of simulations, antagonist inhibition is interrupted by two bursts of neural firing, each of 1 ms duration and separated from each other by 1 ms. Example A is a simulated 15 degree saccade with normal inhibition for purposes of comparison; B–G demonstrate the effects of the altered controller signals as the antagonist bursts are initiated progressively later in the saccadic trajectory. Failure of inhibition of the antagonist can be present even when no fractionation is apparent on the velocity trace as in B and C. Simulations E and F have subcomponents of much shorter duration and higher peak velocity than predicted by the main sequence, but have over-all peak velocities expected for their 10 degree position change. Simulations with other parameters produced saccadic trajectories comparable to the variations of saccades found in our patients' recordings.

At the end of the phasic saccadic component, the abducting eye usually reached the vicinity of the target, while the adducting eye did not. Therefore, the adjusted pulse of innervation from the pulse generator for the binocular refixation movement must have been determined for the abducting eye. The weakness of the adductor did not determine the duration of the pulse of innervation except in the occasional case where the fixing eye was not the abducting eye. This situation will be considered later.

Abducting Nystagmus and Deficient Tonic Inhibition in the Medial Rectus

The abducting nystagmus in our patients' recordings varied in pattern and amount. The initial abducting saccades were hypometric, normometric or hypermetric with about equal frequency. Following this, the abducted eye drifted nasally. After 80 to 200 ms another abducting saccade of lesser amplitude occurred. It, in turn, was followed by another drift. This sequence of abducting saccades and drifts often diminished progressively until the position of the eye became stable.

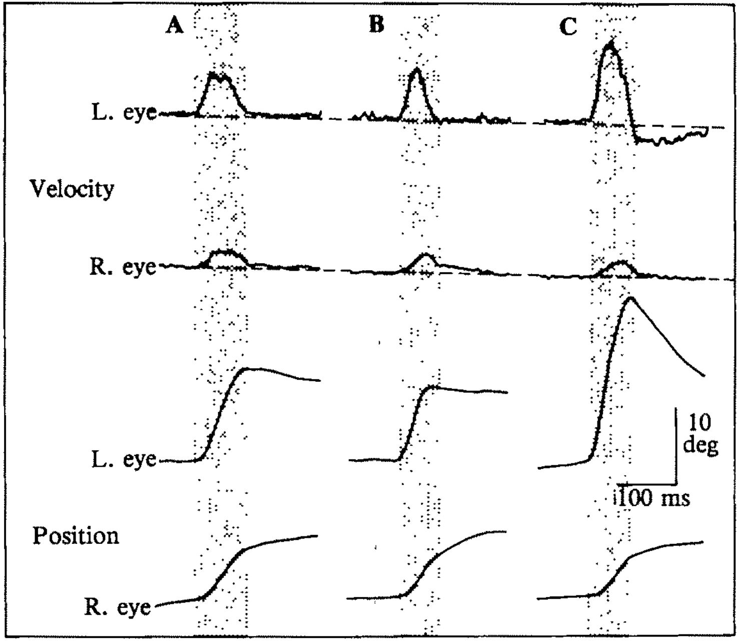

FIG. 7. Binocular recordings of internuclear ophthalmoplegia showing position and velocity of phasic components. Despite the marked decrease in magnitude and velocity of the adducting eye in each case, the duration for abduction and adduction is identical (*shaded areas*). Occasionally, the duration of the phasic components of an adducting saccade may appear to be reduced if the velocity is so slow that a portion of the trace is lost in the noise level of the recording. This may account for the timing delays reported to occur in internuclear ophthalmoplegia (Fricker and Sanders, 1975). Also, adducting velocity may be so slow that duration of the phasic component becomes unmeasurable. Because the duration of the phasic component is usually sufficient to bring the abducting eye to the intended position and the durations of both adducting and abducting phasic saccadic components are equal, the controller signals to move the eye must usually be determined for the abducting eye.

Binocular recording confirmed that the adducting eye also participated in these events providing that the medial rectus muscle had sufficient strength to move the eye. Velocity recordings from the adducting eye revealed low amplitude saccades which were difficult to detect in the position recordings (fig. 8). These were synchronous with the jerks of the abducting nystagmus.

The successive diminution of the drifts between abducting jerks suggested that attempted stepwise, conjugate adjustments of tonic innervation occurred until eye position was stable. We know from electromyographic data that the level of medial rectus tonus remains inappropriately high in lateral gaze. Because the inhibitory control system for the medial rectus is deficient, even reciprocal changes in innervation may result mainly in increased lateral rectus tone. Alternatively, an adjustment only in the level of medial rectus inhibition may occur, leaving agonist tonic excitation unchanged. However, the facilitation of adduction with the abducting nystagmus seen in many of our patients' recordings would not occur.

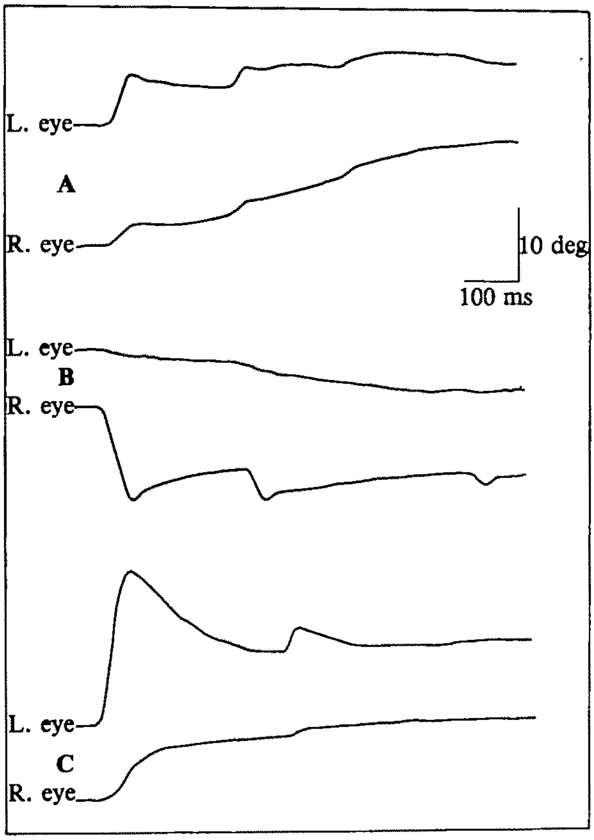

FIG. 8. Binocular recordings from three different patients demonstrate that abducting nystagmus can be A, hypometric, B, normometric, or C, hypermetric. In addition, associated nystagmus of the adducting eye, but of smaller magnitude than the abducting eye is apparent in A and C. Occasionally, these adducting jerks were clearly demonstrable only in the velocity traces.

Therefore, we modelled the abducting nystagmus by increasing agonist tone primarily and decreasing antagonist tone only modestly. Abducting jerks were arbitrarily interposed at 200 ms intervals. The simulated abducting nystagmus is shown in fig. 9.

Unilateral Internuclear Ophthalmoplegia

Oculographic studies did not support unilaterality in our patients with clinical diagnoses of unilateral internuclear ophthalmoplegia. For example, clinically the patient whose record is shown in fig. 10 had a left internuclear ophthalmoplegia. During a 10 degree leftward refixation, the peak velocity in the abducting left eye was almost normal (466 deg s^{-1}), even though the velocity trace was fragmented.

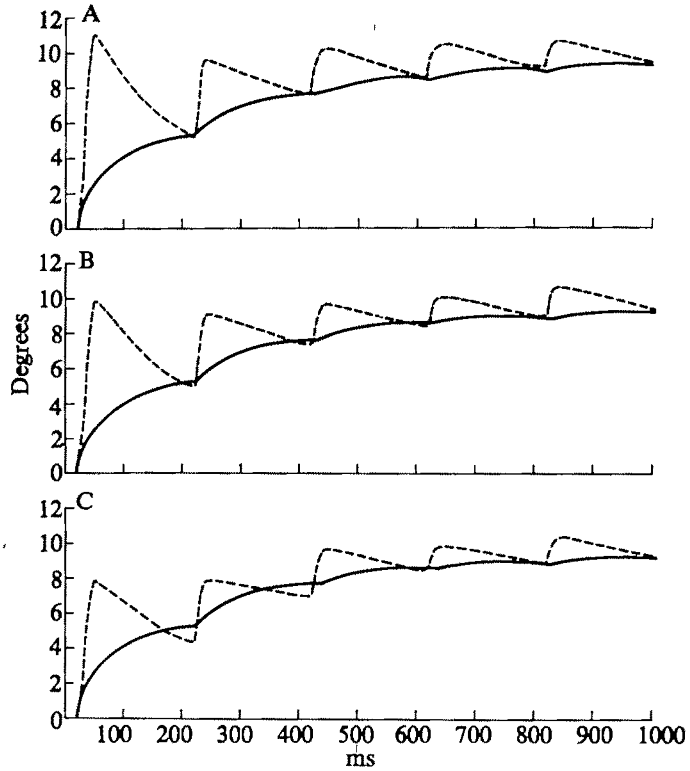

FIG. 9. Computer simulations of binocular eye movements in internuclear ophthalmoplegia. By varying the amount of deficient inhibition of the antagonist medial rectus, hypermetric (A), normometric (B) or hypometric (C) abducting movements can be generated. Following the initial abducting saccade, tone in the medial rectus is maintained at an abnormally high level. However, with each successive abducting jerk, tonus gradually adjusts by reciprocal increases in agonist tone along with some diminution of antagonist tone. This tonic change accounts for the slope of the drift component of the abducting nystagmus which gradually diminishes and would stop altogether if the simulations were carried out further in time. The adducting eye is slow due to reduction in pulse height of the neural controller signal; therefore, only minimal nystagmoid jerks occur in synchrony with the abducting nystagmus. The gradual nasal drift of the adducting eye occurs as a result of decreasing lateral rectus tone, a consequence of the conjugate inhibition by the controller signal to the yoked antagonist medial rectus. If control of antagonist medial rectus tone were not reciprocal, simulated abducting nystagmus would not be altered, but no further nasal drift of the adducting eye would occur after the initial tonic level was achieved.

The peak velocity of the adducting right eye was slightly less, being 411 deg s^{-1}. The durations of the phasic components for both the adducting and abducting eyes were significantly prolonged—54 ms instead of the expected 30 ms. During rightward refixation, the slowing of the left medial rectus was obvious. The abducting right eye was slightly slow (412 deg s^{-1}) and appeared fragmented on the velocity trace. Duration was again significantly prolonged.

This example illustrates that medial rectus excitation and inhibition are deficient bilaterally, excitation being more affected for the left medial rectus. Examination of saccadic duration exposes the increased innervation required for either abducting eye to achieve a given saccadic magnitude. Rightward refixation shows the left

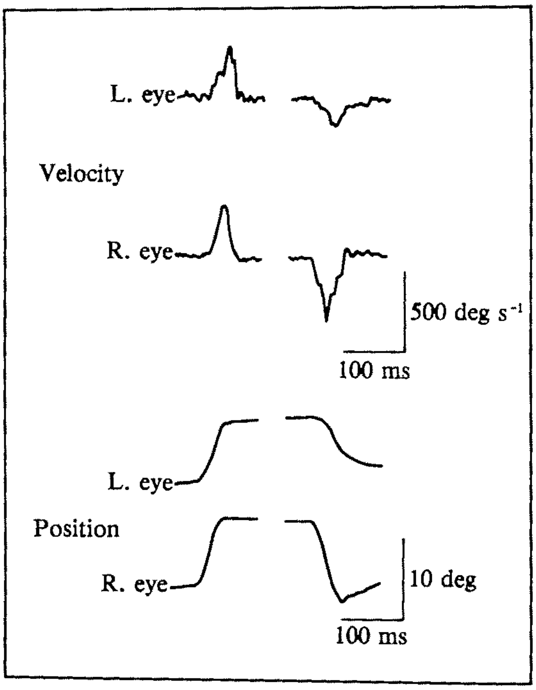

FIG. 10. Position and velocity traces of a patient with predominantly left internuclear ophthalmoplegia. On position traces, leftward movements seem conjugate and relatively fast. Scrutiny of the corresponding velocity traces, however, reveals 'fractionation' in the abducting eye, suggesting a deficiency of medial rectus inhibition. The adducting eye achieves virtually the same peak velocity, but the curve is smooth. Durations for abducting and adducting eye movements are slightly prolonged and peak velocity is somewhat reduced. Rightward movements are disconjugate, demonstrating marked adduction slowing and abduction 'fractionation'. Thus, the internuclear ophthalmoplegia is bilateral, but highly asymmetric. The slight left gaze paresis results from approximately equal deficiencies of medial rectus excitation of the adducting right eye and of medial rectus inhibition of the abducting left eye.

internuclear ophthalmoplegia; however, the defective abduction and adduction on leftward refixation is coincidentally almost equal and produces a slight left gaze paresis. Involvement of the 'left gaze centre' would not account for the fractionation seen on the velocity trace of the abducting eye.

Unilateral Internuclear Ophthalmoplegia with Abduction Lag

Records of some clinically unilateral cases of internuclear ophthalmoplegia showed abduction to be more slowed in the eye with the more severe medial rectus deficiency (fig. 11). The severe fractionation of the abducting saccade apparent on both position and velocity traces in fig. 11B suggests a profound deficiency of inhibition to the left medial rectus. Thus, when the internuclear ophthalmoplegia is asymmetric, varying the amount of deficient medial rectus inhibition and excitation can produce the appearance of internuclear ophthalmoplegia, conjugate gaze paresis or abduction lag.

This variation in innervation is most striking in the patient whose record is shown in figs. 11B and 12. Because this patient had a dense amblyopia in the left

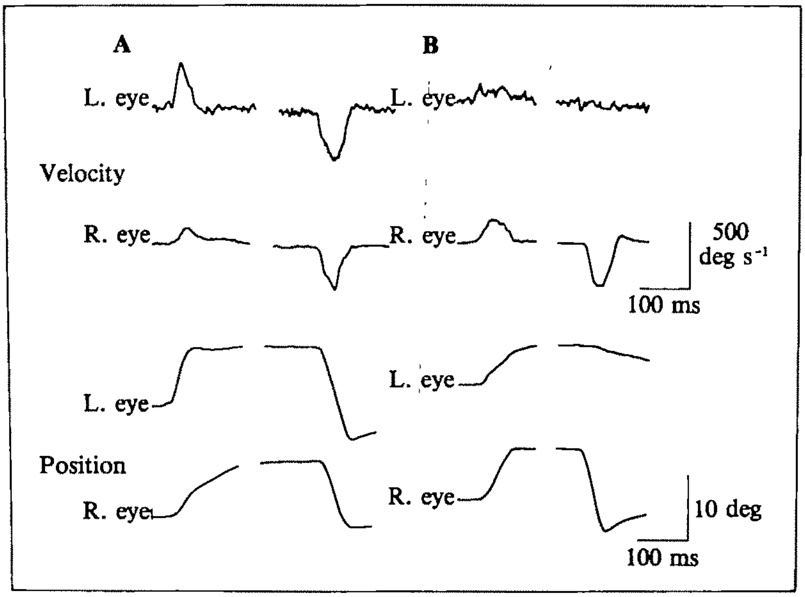

FIG. 11A, predominantly right internuclear ophthalmoplegia apparent on left gaze with an associated mild abduction lag on right gaze. In this case the deficiency of medial rectus inhibition of the right eye exceeds the deficiency of excitation of the left eye. The abducting eye reaches the target, while the left eye appears to overshoot. B, prominent abduction lag of the left eye on left gaze, the same eye which demonstrates the most marked adduction weakness. This case (6) is unusual in that the left eye is amblyopic (20/200); therefore, the controller signal for eye movement has apparently been adapted such that the right eye reaches the vicinity of the target. Prolonged duration of the right eye on left gaze is a consequence of the additional innervation required for this to occur and exposes the deficiency of adduction.

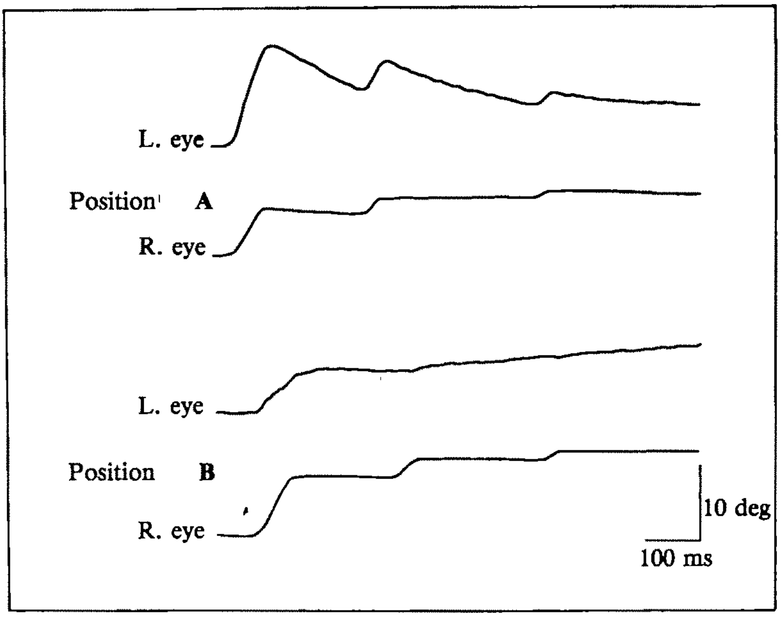

FIG. 12. Records of two refixation movements from the same patient (Case 6) as was shown in fig. 11B. The rapid change in antagonist medial rectus function on abduction of the left eye is demonstrated by these two traces recorded within a minute of each other. In example A the abduction is hypermetric with prominent nystagmus. In example B the deficiency of abduction is pronounced and the abducting jerks are not apparent. The similarity of the adduction traces in A and B lend additional support to the suggestion that the adducting eye determines the innervation in this unusual patient with amblyopia of the left eye.

eye, refixations were programmed by the right eye. The right eye reached the target after a few correcting saccades. In the lower tracing of fig. 12, abduction is severely slowed; however, abduction in the upper tracing is hypermetric, presumably due to more adequate reciprocal inhibition by the left medial rectus. The increased conjugate innervation required to put the adducting eye on target is reflected by the overshoot of the abducting eye.

Summary of Findings

The main oculographic findings in our patients with internuclear ophthalmoplegia were attenuated phasic and tonic forces of adduction, fractionated phasic saccadic components in abduction, equal durations for the phasic portions of both adducting and abducting saccades, and nasal drift of the abducting eye which appeared to initiate the abducting jerks. In addition, gaze paresis and abduction lag were associated with primarily unilateral cases of internuclear ophthalmoplegia on gaze to the side of the paretic medial rectus. All oculographic findings and computer simulations were most consistent with the hypothesis that deficient excitation and inhibition of the medial rectus was present under both phasic and tonic conditions.

DISCUSSION

Deficiency of Medial Rectus Excitation

Lesions of the medial longitudinal fasciculus have been shown pathologically and experimentally to result in deficient excitation of the ipsilateral medial rectus (Christoff, Anderson, Nathanson and Bender, 1960; Evinger, Fuchs and Baker, 1977; Carpenter and McMasters, 1963; Burde, Lehman, Roper-Hall, Brooks and Keetner, 1977). The exact neuronal basis for the deficient excitation of the medial rectus was elucidated physiologically by Highstein (1976) and anatomically by Graybiel and Hartweig (1974) and Büttner-Ennever and Henn (1976). They found that interneurons in the contralateral abducens nucleus crossed immediately and then projected to the medial rectus subnucleus of the oculomotor complex *via* the medial longitudinal fasciculus.

Burst-tonic units mediating horizontal eye movements are commonly isolated in microelectrode studies of the medial longitudinal fasciculus (Pola and Robinson, 1978; King, Lisberger and Fuchs, 1976). Deficiency of medial rectus excitation is likely to be due to damage of these axons. Therefore, the alteration of the saccadic controller signal in internuclear ophthalmoplegia must be primarily a reduction in pulse height rather than a decrease in pulse width. The slow and incomplete adduction can be attributed to a deficient tonic level of medial rectus innervation. This interpretation is consistent with the results of other oculographic studies (Bird and Leech, 1976; Kirkham and Katsarkas, 1977; Baloh *et al.*, 1978) as well as our own (fig. 2).

Deficiency of Medial Rectus Inhibition in Abduction

The use of high resolution techniques for recording eye movements allowed us to make observations not previously recognized in internuclear ophthalmoplegia. Most important was the identification of fractionated abducting saccades (fig. 4). Although overlapping saccades have been reported during moderate fatigue in normal subjects, the duration and peak velocity of each of these saccades was normal. Bahill and Stark (1975) explained double saccades as a decompensation occurring prior to the 'time optimal pulse-width shaping mechanism' in the brainstem. However, the fractionated abducting saccades described here had subcomponents which were often of too short a duration and too rapid a velocity (fig. 5) to have been generated by decompensation at such a high level. Therefore, we considered lower level internuclear mechanisms which might disrupt the already formed pulse-step of innervation.

The electromyographic data recorded by Loeffler and associates (1966) and by Gonzalez and Reuben (1967) showed that deficiency of tonic inhibition of the medial rectus was present ipsilateral to the side of the adduction weakness in unilateral cases. The resolution of their published records does not permit any detailed evaluation of deficient medial rectus inhibition during the phasic portion of the abducting movement. Deficient inhibition, however, seems to be present in the electromyographic tracings published by Huber and Esslen (1972). Using computer simulations, we were able to determine precisely how deficient inhibition during phasic components of abducting saccades accounts for our oculographic findings (fig. 6).

Differing Binocular Oculographic Patterns Associated with Internuclear Ophthalmoplegia

Increased variability in the peak velocities of abducting movements in internuclear ophthalmoplegia was reported by Kirkham and Katsarkas (1977). We found variable slowing of both adduction and abduction in internuclear ophthalmoplegia, a fact previously emphasized by Bird and Leech (1976). These differences in adducting and abducting saccadic velocities combined to give several different binocular oculographic patterns associated with internuclear ophthalmoplegia.

Internuclear ophthalmoplegia with gaze paresis. We have shown that minimal abduction slowing is common in oculographic recordings which conform to the pattern of internuclear ophthalmoplegia. Occasionally, we found records in which the simultaneous occurrence of mild medial rectus weakness in the adducting eye and deficient antagonist medial rectus inhibition in the abducting eye produced a gaze paresis (fig. 10). This explanation accounts for the fractionation seen in the abducting saccades, a finding which cannot be due to involvement at or above the level of the pulse-shaping mechanism. Therefore, the lesion which produces ipsilateral gaze paresis in predominantly unilateral internuclear ophthalmoplegia may be limited to the area of the medial longitudinal fasciculus. Of course, in any given case with severe gaze palsy (excluded from this study), gaze mechanisms could be involved directly (Enoksson, 1965; Fisher, 1967; Balthasar, 1973).

Internuclear ophthalmoplegia with abduction lag. As shown in our study and others (Kirkham and Katsarkas, 1977), when antagonist medial rectus inhibition is severely deficient, abduction lag may occur in predominantly unilateral cases of internuclear ophthalmoplegia. Kommerell (1975) proposed that the term internuclear ophthalmoplegia of abduction should be reserved for those cases of abduction lag in which static positions of gaze are normal. He presented a case of bilateral abduction lag in which adduction of each eye was 'about normal'. He suggested the lesion be localized to a region between each abducens nucleus and each paramedian pontine gaze centre. The equipment used in his study differed from ours, so the maximum recorded velocity of adduction of less than 500 deg s^{-1} for a 20 degree saccade may either be normal or may suggest some bilateral adduction weakness. Though we do not have an example of bilateral internuclear ophthalmoplegia of abduction, the unilateral cases of abduction lag shown in fig. 11 demonstrate the fractionation of the abducting saccades which we believe to be indicative of deficient inhibition of the medial rectus. Therefore, internuclear ophthalmoplegia of abduction may represent a lesion involving the medial longitudinal fasciculus in which the abduction slowing from deficient medial rectus inhibition of one eye exceeds adduction slowing from the deficient medial rectus excitation of the other eye.

In fig. 12, a fortuitous recording documents the change from an internuclear ophthalmoplegia of abduction to a typical internuclear ophthalmoplegia occurring in the same patient, minutes apart. Kirkham and Katsarkas (1977) documented a similar change from adduction lag to abduction lag in one of their patients over a six-month period and suggested that the change was due to a conjugate repair process. Kommerell's case (1975) was recorded several years after the initial brain insult. If, for some reason, inhibitory pathways are affected more severely or are repaired more slowly than excitatory ones, again a lesion involving the medial longitudinal fasciculus could account for all the findings in internuclear ophthalmoplegia of abduction.

Altered binocular innervation in internuclear ophthalmoplegia. We have shown several binocular oculographic patterns found in patients with internuclear ophthalmoplegia, depending upon the variability in medial rectus innervation for each eye. If medial rectus excitation was more deficient than medial rectus inhibition of the opposite eye, then a typical internuclear ophthalmoplegia resulted. If the amount of medial rectus excitation was about equal to the amount of medial rectus inhibition of the opposite eye, then a gaze paresis occurred. Finally, if medial rectus excitation was less deficient than medial rectus inhibition of the opposite eye, then abduction lag resulted in the oculographic appearance of internuclear ophthalmoplegia of abduction.

Proposed Mechanism for Abducting Nystagmus in Internuclear Ophthalmoplegia

Can we construct a mechanism for the production of abducting nystagmus based upon our oculographic observations? We confirmed the clinical and oculographic findings of others (Baloh *et al.*, 1978) that adduction jerks can be associated with abducting nystagmus when the degree of medial rectus weakness is not severe. This suggested that the nystagmus is generated initially as a conjugate saccadic movement, the adducting component being degraded secondarily. Additionally, we found that the slope of the slow phase of the nystagmus became progressively less steep. As proposed in the Results and Analysis section, this gradual change in tonic forces could either be due to a slow decrease in tone of the antagonist or to a reciprocal readjustment of agonist-antagonist tone. The latter alternative is supported by the continued drift of the adducting eye toward the target with continued abducting nystagmus. Presumably this drift of the adducting eye is a consequence of the increased tone of the yoked lateral rectus (agonist) and the decreased tone of the yoked medial rectus (antagonist) of the abducting eye. Such tonic adjustments are also suggested by electromyographic studies (Huber and Esslen, 1972).

Saccadic abducting jerks may occur because changes in tonic forces are facilitated following a pulse-step of innervation or because of internal or external feedback conditions (Pola and Robinson, 1976). The pattern continues so long as the tonic level in the abducting eye is inappropriate to the desired end-position of the abducting eye. We observed that the saccadic amplitudes of successive fast phases of the nystagmus gradually decreased and often stopped altogether when the correct level of tonic activity was achieved, resulting in a non-drifting eye position. This could be an immediate controlled visual behaviour or a long-term adaptive behaviour (Pola and Robinson, 1976; Baloh *et al.*, 1978). Alternatively, 'pauser' cells (Keller, 1977) could be poorly suppressed, temporarily interrupting saccades which then go to completion after proper inhibitory control is restored. Another mechanism not requiring feedback, involves inappropriate gating of signals to the collicular saccadic motor cells which results in the production of multiple saccades (Schiller, 1972). Whichever feedback, adaptive, or pre-programmed mechanism is operating in order to adjust the size of abducting saccades, the combination of increased medial rectus tone and its modification by pulse-steps of innervation is sufficient to account for the findings in abducting nystagmus as demonstrated by the computer simulations in fig. 9.

Previous Models of Abducting Nystagmus in Internuclear Ophthalmoplegia

How does our explanation of abducting nystagmus compare with those of previous investigators? Previous concepts can be divided into those which do not depend upon deficient inhibitory control mechanisms (1, 2) and into that which does (3).

(1) Stroud, Newman, Keltner and Gay (1974) proposed a quasi-vergence mechanism, presumably with normal inhibition. They demonstrated in their patients that asymmetric vergence could modify the abducting nystagmus of internuclear ophthalmoplegia. Increasing convergence with base out prism increased the amplitude of the nystagmus, while decreasing convergence with base in prism decreased the nystagmus. This vergence concept, though, does not sufficiently explain the clinical findings because abducting nystagmus occurs in the dark (Baloh *et al.*, 1978) and with poor acuity, situations in which there is no stimulus for convergence. Also Kommerell and Jaedicke (1972) have shown that abduction nystagmus can occur during lateral gaze in patients with convergence spasm. Pola and Robinson (1976) objected to the vergence concept on similar grounds. Though Stroud and associates demonstrated that normal vergence-induced effects on nystagmus are operative in patients with internuclear ophthalmoplegia, there is no compelling rationale to consider vergence in the generating mechanism of internuclear ophthalmoplegia.

(2) Baloh *et al.* (1978) also proposed a mechanism for internuclear ophthalmoplegia which would not depend upon deficient inhibitory control. Because their oculographic findings documented overshooting abducting saccades and persisting abducting nystagmus in total darkness, they proposed that an adaptive mismatching of the pulse and step signals from the paramedian pontine reticular formation was taking place. Asymmetric slowing of the two eyes would cause visual blur. To minimize this blur, the velocity of the adducting eye would need to be increased. The oculomotor system would then adaptively increase innervation to the medial rectus motor neurons by increasing pulse duration. This adaptive change would cause a mismatch in the pulse and step inputs to the abducens nucleus and would explain the overshoots seen in the abducting eyes of their patients. After a period of time the adaptation would become independent of visual input. Kirkham and Katsarkas (1977) suggested a similar conjugate recalibration or repair mechanism.

Although the above model proposing 'pulse-step mismatch' as the primary mechanism underlying the abducting nystagmus in internuclear ophthalmoplegia is attractive, it is unable to account for our data. We found that hypometric, normometric and hypermetric abducting saccades occurred with about equal frequency. This result would not be anticipated by the 'mismatch' model because the adaptation of the pulse-step of innervation to the weak adductor should always cause overshoot of the normal yoked abducting eye.

Even if we add deficient inhibition of the antagonist medial rectus or direct involvement of the abducens motor neurons to the Baloh and associates' proposal in order to account for the varying magnitude of the abducting saccades, adaptation to a deficient adductor would remain an unlikely mechanism for producing abducting nystagmus. We have shown that phasic components of both adducting and abducting saccades are of equal duration for a given refixation movement (fig. 7). These durations are always at least slightly prolonged, even for the faster abducting eye. Nevertheless, the amount of innervation usually brings the abducting eye to the vicinity of the new target position, regardless of the amount of medial rectus weakness in the adducting eye. Therefore, saccadic duration must usually be determined by the abducting eye. Adaptation to adduction weakness would lead to grossly hypermetric saccades, which seldom occur. Only when the abducting eye is a non-fixing eye, such as that shown in fig. 12B, might pulse-step mismatch play a primary role. Nevertheless, substantial deficiency of medial rectus inhibition still plays some role by causing abduction lag rather than overshoot in fig. 12.

The fairly accurate refixations of abducting eyes suggest that the pulse generator has adapted to the increased tone against which the lateral rectus must pull by increasing pulse width. An adaptive change of pulse width rather than pulse height is necessary since all neurons fire maximally for saccades larger than a few degrees as determined electrophysiologically (Keller, 1974) and by time-optimal control studies (Cook and Stark, 1968; Clark and Stark, 1975). Hence, the trajectory of the abducting saccade may be determined by long-term adaptation to an average state of deficient inhibition of the antagonist medial rectus as well as the variation in the amount of deficient antagonist inhibition in any given saccade.

Our evidence shows that the pulse-step of innervation is usually programmed for the abducting eye. Thus, hypotheses which rely primarily upon pulse-step mismatches programmed by the weak adducting eye are not supported.

(3) Pola and Robinson (1976) were aware of the possible primary role of deficient medial rectus inhibition in their formulation of a model for abducting nystagmus in internuclear ophthalmoplegia. Because firing of neural units in the medial longitudinal fasciculus does not occur during abduction of the ipsilateral eye, Pola and Robinson proposed that inhibitory medial longitudinal fasciculus neurons may innervate the contralateral medial rectus subnucleus. A lesion in the medial longitudinal fasciculus could thereby result in increased tone to the contralateral medial rectus subnucleus and cause the eye to turn in. The ipsilateral eye would turn out because of the deficient excitation. This would lead to an adaptive realignment of tonic forces in order to keep the eyes in primary position. As a consequence, the neural signal to the abducting eye would be a slightly small pulse with a disproportionately small step. Oculographically, the appearance would be a necessarily hypometric refixation followed by a drift toward primary gaze which in turn would elicit a corrective abducting jerk.

The Pola and Robinson model is able to explain both the adduction weakness and the abducting nystagmus by a single lesion within the medial longitudinal fasciculus. However, we and others (Kirkham and Katsarkas, 1977; Baloh *et al.*, 1978) have already pointed out that hypermetric abducting saccades occur commonly. Therefore, some mechanism other than 'conjugate bias' must be primarily involved in the production of the abducting nystagmus. In addition, such a 'tonic' model could not account for the alteration of the phasic components of abducting saccades reported here (fig. 4). Finally, there is no evidence to support inhibitory pathways within the medial longitudinal fasciculus.

Possible Inhibitory Pathways Affected in Internuclear Ophthalmoplegia

On the basis of oculographic, electromyographic and computer modelling data, we believe that deficient inhibition of the medial rectus during phasic and tonic components of abducting saccades is a significant finding and should be included in any comprehensive explanation of internuclear ophthalmoplegia. However, neurophysiological and neuroanatomical data regarding inhibitory pathways are limited. Proposed inhibitory pathways to the medial rectus motor pool can be divided into those which travel from the region of the abducens nucleus (long pathways) and those which arise in the region of the third nerve nucleus (short pathways).

Long pathways. Inhibitory neurons within the long pathways could either travel within the medial longitudinal fasciculus or parallel to it. Also, the inhibitory innervation could either be ipsilateral or contralateral to the excitatory input. Inhibitory neurons within the medial longitudinal fasciculus on the side of the internuclear ophthalmoplegia have not been found (Keller, 1974; King *et al.*, 1976; Pola and Robinson, 1976, 1978), though a contralateral inhibitory pathway within the medial longitudinal fasciculus has been proposed by Pola and Robinson (1976).

Para-medial longitudinal fasciculus inhibitory pathways could run close enough to the medial longitudinal fasciculus so that they would almost always be involved in internuclear lesions. Büttner-Ennever and Henn (1976) described a pathway arising from the para-pontine reticular formation which emerged just lateral to the nucleus centralis superior at the level of the trochlear nucleus. It ascended close to the midline, just ventral to the medial longitudinal fasciculus and surrounded the rostral border of the ipsilateral oculomotor nucleus and its outgoing rootlets. This pathway was previously described by Goebel, Komatsuzaki, Bender and Cohen (1971). Büttner-Ennever and Henn (1976) also cited Cajal as demonstrating that 'the peri-OMN (peri-oculomotor nucleus) axons certainly pass through the wide dendritic field of oculomotor neurones'. Alternatively, since we found evidence of bilateral deficiency of inhibition in all our cases, the inhibitory pathway might run in the midline rather than laterally or ventrally. Support for this is provided in a recent report by Keller (1977) that 'pauser' cells, which inhibit oculomotor neuron firing during saccades in all directions, are localized to the midline of the upper pons.

Hikosaka and Kawakami (1977) recorded intra-cellularly from interneurons lying caudally to abducens nucleus that crossed and were inhibitory to contralateral abducens motoneurons (Grantyn and Grantyn, 1976; Destombes, Gogan and Rouviere, 1979). Testing with antidromic stimulation from motor nerve could establish that this inhibition is also produced at the 'surrogate motoneurons' which excite and disfacilitate the opposite medial rectus motoneurons.

Short pathways. Short inhibitory pathways to the medial rectus subnucleus of the oculomotor complex can only project contralaterally. Henn and Cohen (1972) described inhibitory interneurons found amongst agonist motor neurons which discharged only with eye movements away from the muscle innervated by the particular subnucleus—so called 'mirror' units.

Another possible short pathway might be recurrent collaterals from medial rectus motoneurons projecting contralaterally *via* inhibitory interneurons similar to the Renshaw cells of the spinal cord; this speculation is supported by recent anatomical studies (Evinger, Baker and McCrea, 1979). However, physiological and anatomical data may be in conflict with this hypothesis (Sasaki, 1963; Eccles, Eccles and Lundberg, 1958; Precht, Richter and Grippo, 1969). Also, this alternative would first require divergence with later convergence of the inhibitory signal in order to allow for quantitative differences between excitatory and inhibitory deficiencies (Stark, Semmlow and Terdiman, 1968).

If a determination could be made as to whether medial rectus inhibition is conducted ipsilaterally or contralaterally, then the number of possible pathways could be substantially reduced. Using the fractionated velocity trace seen on abduction as a marker for deficient inhibition of the medial rectus, however, could not provide an answer, because we were unable to find a single strictly unilateral case. Several cases (Table 1) which appeared clinically to be unilateral had slowed adduction and fractionated, prolonged abducting saccades bilaterally when analysed oculographically. In the traces of many asymmetric bilateral internuclear ophthalmoplegias (such as those in fig. 11), the fractionation of abducting saccades was more marked ipsilateral to the more severe medial rectus weakness. Ipsilateral inhibitory pathways might also be more consistent with the electromyographic findings of unilateral internuclear ophthalmoplegia (Loeffler *et al.*, 1966).

On the basis of ipsilaterally mediated deficiency of inhibition of the medial rectus in abduction, we could construct the oculographic appearance of a truly unilateral internuclear ophthalmoplegia. For a right internuclear lesion, leftward refixations should have normal durations for the phasic saccadic components for each eye and the abducting eye should be normometric without abducting nystagmus. Adduction would be poor. Rightward refixation movements should be prolonged equally in each eye as a higher level adaptation to the average increase in phasic antagonist tone. Abducting saccadic magnitudes and peak velocities would be variable. Conjugate nystagmus would be present. Adduction in rightward movements should be hypermetric and of appropriate velocity if the right eye is fixing, entirely normal if the left eye is fixing. In contrast, any of the proposed contralateral inhibitory pathways would predict hypometric saccades with appropriate velocities of the abducting eye on left gaze and would be associated with abducting nystagmus. Refixation movements to the right would be entirely normal in each eye. Final determination of the inhibitory pathway to the medial rectus subnucleus of the oculomotor complex must await further oculographic, electromyographic and neuroanatomical investigation.

SUMMARY

High resolution infra-red oculographic recordings were obtained in 19 patients with clinically evident internuclear ophthalmoplegia. The major findings were

attenuated phasic and tonic components of adducting saccades, fractionated phasic components of abducting saccades, equally long durations for phasic components of adducting and abducting saccades with refixation, and nasal drift of the abducting eye which initiated abducting nystagmus. Ipsilateral gaze paresis and abduction lag were occasionally associated with primarily unilateral cases of internuclear ophthalmoplegia. These findings were interpreted using available anatomical, electromyographic and oculographic data as well as computer simulations of internuclear ophthalmoplegia.

We concluded that deficient excitation of the ipsilateral medial rectus was due to interruption of burst-tonic neurons within the medial longitudinal fasciculus which mediate horizontal eye movements. This resulted in a decreased pulse height and step of the agonist neural controller signal. We were also able to determine that variably slowed fractionated abducting saccades were caused by deficient intrasaccadic inhibition of the antagonist medial rectus.

When medial rectus excitation was more deficient than medial rectus inhibition of the opposite eye, then a typical internuclear ophthalmoplegia resulted; when the amount of medial rectus excitation was equal to the amount of medial rectus inhibition of the opposite eye, then a gaze paresis occurred; and when medial rectus excitation was less deficient than medial rectus inhibition of the opposite eye, abduction lag resulted in the oculographic appearance of internuclear ophthalmoplegia of abduction.

Abducting nystagmus appeared to be initiated by a tendency for the abducted eye to drift nasally from the increased level of tonic inhibition of the antagonist medial rectus.

Some oculographic patterns were attributed to higher level adaptive changes in innervation. These changes were a consequence of disordered excitatory and inhibitory controller signals at the lower, internuclear level. Possible anatomical pathways which might carry these inhibitory controller signals were discussed.

High resolution eye movement recordings of patients with internuclear ophthalmoplegia were interpreted directly and by computer simulations as being most consistent with disordered inhibitory and excitatory control of the medial rectus motor pool during rapid eye movements and eccentric gaze.

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VARIABILITY OF VISUAL THRESHOLD IN MULTIPLE SCLEROSIS

EFFECT OF BACKGROUND LUMINANCE ON FREQUENCY OF SEEING

by V. H. PATTERSON, D. H. FOSTER *and* J. R. HERON

(*From the Department of Neurology, North Staffordshire Hospital Centre, Stoke-on-Trent, and the Department of Communication and Neuroscience, University of Keele, Staffordshire*)

INTRODUCTION

A VISUAL threshold is the minimum luminous intensity of a light stimulus necessary for its perception. It is one of the simplest and most fundamental properties of visual function and one which depends on the integrity of the visual system from cornea to cortex. In clinical practice visual thresholds may be measured by static perimetry with a Goldmann or Tübinger perimeter. The intensity of the light stimulus is increased until it is perceived by the subject, this intensity value being taken as the threshold. Repeated testing of the same point by this method produces a normal variability of within 0.3 to 0.4 log units of light intensity (Ellenberger, 1974).

It is hardly surprising that visual thresholds are sometimes elevated in multiple sclerosis (MS), a disease in which the visual pathway is frequently affected. Raised thresholds have been reported by Burde and Gallin (1975) in the affected eyes of patients with previous retrobulbar neuritis. Harms (1976) not only found raised thresholds in patients with recovering retrobulbar neuritis, but also noted excessive scattering of thresholds on repeated testing at the same point.

We too have found retinal sites in patients with MS at which threshold shows increased variability, but have noticed that this variability seems to be most marked when the patients are examined at high background luminance levels. In order to elucidate this, we have quantified threshold variability and determined how it is affected by background luminance in MS patients and control subjects.

SUBJECTS

Five patients with multiple sclerosis (MS), in whom abnormally variable visual thresholds had been noted, were selected for study. Three patients had clinically definite MS and two had probable MS, according to the diagnostic criteria of

Rose, Ellison, Myers and Tourtellotte (1976). None of the eyes tested had ever had visual symptoms but all had subclinical optic neuropathy as evidenced by nerve-fibre bundle defects on tangent screen examination of the visual fields (V. H. Patterson and J. R. Heron, in preparation). Optic discs were all judged to be normal. Further details are given in Table 1.

Five subjects without evidence of MS acted as controls. Four were members of hospital staff and the other was a patient with a radial nerve palsy. All but two were unaware of the purpose of the experiment. They showed a similar distribution of age, sex and refractive error as the patients. Informed consent was obtained from all subjects.

TABLE 1. DETAILS OF PATIENTS

Case	*Sex*	*Age (yrs)*	*Classification*	*Clinical manifestations*	*Duration (yrs)*
1	M	32	Clinically definite	Optic neuritis. Relapsing and remitting paraparesis.	8
2	M	41	Clinically definite	Progressive paraparesis. Subclinical optic neuropathy.	7
3	M	26	Clinically definite	Relapsing and remitting cerebellar and spinal signs. Subclinical optic neuropathy.	3
4	F	24	Probable	Recurrent ataxia. Subclinical optic neuropathy.	5
5	M	28	Probable	Lhermitte's sign. Persistent visual symptoms with signs.	1

PROCEDURE

Subjects sat in a chair with a firm headrest and viewed a circular white screen of diameter 0.6 m at a distance of 1.6 m through an adjustable eyepiece. Spectacles were worn if appropriate and the eye not being tested was occluded. An artificial pupil was not used. Subjects fixated a small target at the centre of the screen. The screen was illuminated by two pairs of 100 W incandescent lamps powered by a stabilized d.c. supply which at 250 V gave a uniform screen luminance of 3.0 log cd m^{-2}. Neutral density filters of 1.0 and 2.0 log units could be placed in front of the subject's eye to give apparent screen luminances of 2.0 and 1.0 log cd m^{-2}, respectively. For zero background luminance the screen was covered with black material, and the subject fixated the centre of an array of four small white lights. The stimulus flash was provided by a red light-emitting diode (LED) of peak emission wavelength 635 nm (type MV 5752), the time course and intensity of which was controlled by suitable electronics. The LED subtended 11 minutes of arc at the subject's eye. Flash duration was fixed at 20 ms, and flash intensity was controlled by the experimenter. In preliminary measurements on patients, retinal sites in each quadrant at 5 deg eccentricity and about 45 deg inclination from the horizontal meridian were examined at a background luminance of 3.0 log cd m^{-2} to determine the site at which visual threshold seemed most variable. This was then selected for further study. Similar measurements in normal subjects had not shown any difference in variability between different retinal quadrants. Each subject was tested in two sessions of about one hour each, which were usually held on successive days. In the first session the subject was tested at a background luminance of 3.0 log cd m^{-2} and then, after dark-adaptation for 30 minutes, tested at zero background luminance. In the second session, the subject was dark-adapted for 20 minutes and then tested at background luminances, first of 1.0 log cd m^{-2}, and then of 2.0 log cd m^{-2}. The order in which the background luminances were presented was found not to be critical since similar results were obtained when the order was changed. Fixation was not specifically monitored, but all the patients had consistently identified the blind spots on visual field testing, and none had nystagmus.

A frequency-of-seeing curve was constructed for each subject at each background luminance as follows. An approximate threshold value for the stimulus flash was determined by a method of limits (Engen, 1971). Ten consecutive intensity settings at 0.1 log-unit intervals were then selected with the approximate threshold value in the middle of the range, and flashes of these intensities were presented to the subject in a random order. The subject controlled the onset of the flash by means of a push-button switch and indicated after each presentation whether or not he had seen the flash. After a rest period of 30 seconds, the ten flashes were presented in a different order, and this procedure was repeated until each flash of a given intensity had been presented 10 times. The sequence of presentations of the flashes was predetermined and was balanced for order and residual (carry-over) effects (Finney, 1960). The frequency-of-seeing at each stimulus intensity was then calculated, and a frequency-of-seeing curve was constructed.

We used the classical method of constructing a frequency-of-seeing curve in preference to a two-interval forced-choice technique (Tanner and Swets, 1954; Nachmias, 1972), after carrying out preliminary experiments in which both methods were used. The results obtained by the two methods were similar but the two-interval forced-choice technique was more time-consuming because of the number of blank presentations involved, and subjects preferred the conditions of the classical method.

STATISTICS

The frequency-of-seeing curves were analysed by computer probit analysis (Finney, 1952). This procedure assumes that the sigmoid nature of the frequency-of-seeing curve is determined by an underlying normal distribution; the mean of this distribution is the intensity ΔI_{50} at which a stimulus is seen 50 per cent of the time, and the standard deviation σ of the distribution corresponds to the variability in seeing. This assumption of underlying normality is not intended here to have any theoretical significance (Blackwell, 1963); it is used merely as a means of quantifying the frequency-of-seeing data. The mean values of ΔI_{50} and σ for the patient group were compared with those for the control group using Student's t test.

In order to determine whether fatigue effects (Sunga and Enoch, 1970) occurred over the course of the experiment or within the groups of ten presentations, we computed the number of positive responses for each group and for each position within the groups at the two highest background luminances. Correlation coefficients and regression lines for the trends in these numbers were obtained in all subjects, and their significance calculated using a t test.

RESULTS

Computer-fitted frequency-of-seeing curves from a representative patient and control are shown in fig. 1. In the control subject the slope of the curve is substantially the same at all background luminances although there is a small increase with the introduction of the background. In the patient, however, there is a striking progressive decrease in slope with increasing background luminance.

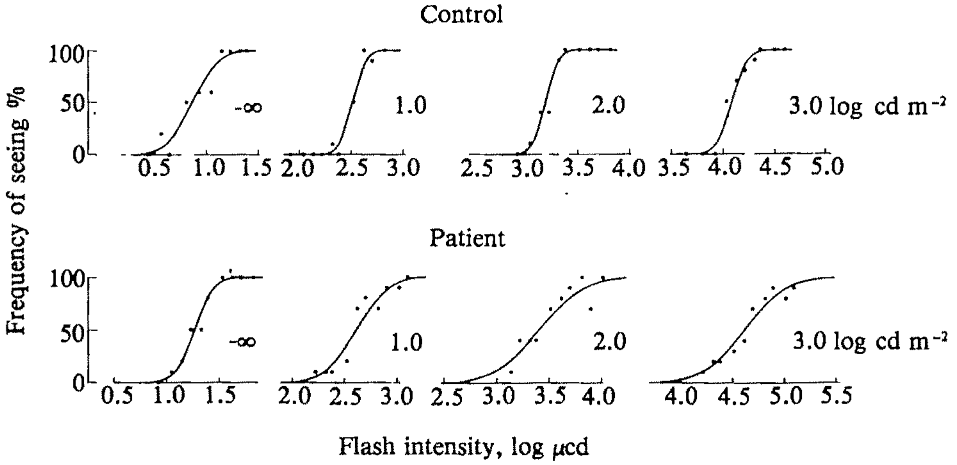

FIG. 1. Frequency-of-seeing curves for a representative patient and control. Each data point is derived from ten trials and the smooth curves are fitted by computer probit analysis. The background luminance for each curve is indicated.

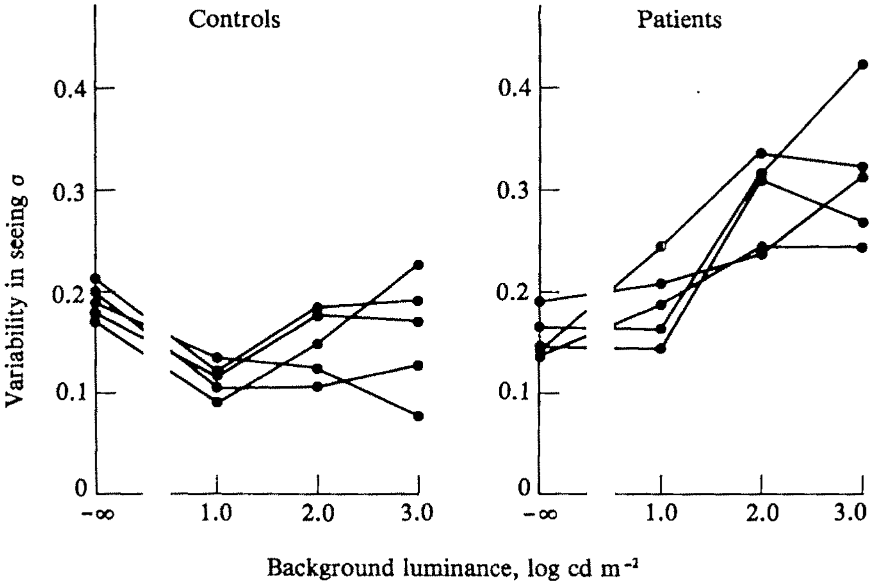

FIG. 2. Variability in seeing obtained by probit analysis plotted against background luminance for individual patients and controls.

When the data are subjected to probit analysis and the variability in seeing σ is plotted against background luminance, significant general differences between the patient and control groups are seen (fig. 2). First, variability for the patient group is slightly less than that of the control group at zero background luminance ($t = 2.74$, $df = 8$, $P < 0.05$), but is significantly greater at 1.0 log cd m^{-2} ($t = 4.01$, $df = 8$, $P < 0.01$), 2.0 log cd m^{-2} ($t = 5.06$, $df = 8$, $P < 0.001$) and 3.0 log cd m^{-2} ($t = 3.86$, $df = 8$, $P < 0.01$), there being no overlap between the two groups at these three non-zero luminances.

Secondly, when variability at zero background luminance and at 3.0 log cd m^{-2} is compared in each group, there is no significant difference for the control group ($t = 1.20$, $df = 8$, $P > 0.2$) but a highly significant difference for the patient group ($t = 4.84$, $df = 8$, $P < 0.01$). Thirdly, the initial fall in variability between zero background and 1.0 log cd m^{-2}, shown by the control group ($t = 7.35$, $df = 8$, $P < 0.001$) is not shown by the patient group ($t = 1.63$, $df = 8$, $P > 0.1$).

The 50 per cent seeing intensities ΔI_{50} for the two groups differ significantly only at the highest background level, 3.0 log cd m^{-2} ($t = 3.22$, $df = 8$, $P < 0.05$). A significant fatigue effect was found in only 3 of the 20 measurements in the patients and in only 2 of the 20 measurements in the controls.

DISCUSSION

Our findings concerning variability of seeing in the control subjects are in close agreement with those of Mueller (1951). Using a foveal stimulus he found no change in threshold variability (as measured by the reciprocal of the slope of the frequency-of-seeing curve) at most levels of background luminance, and he noted a rise in variability at very low light levels, an effect also reported by Blackwell (1963).

Our results in the MS patients differ in several respects from those in the control subjects. First, they confirm and quantify the abnormal variability reported by Harms (1976) and secondly, they show that abnormal variability may occur in conjunction with a normal threshold value (as determined by the 50 per cent seeing intensity). This suggests that in MS, threshold variability is a more sensitive indicator of visual pathway damage than the usual measure of mean threshold. The most important finding, however, is that variability in seeing increases with background luminance in the MS patients. Such an effect would be explained if the transmission of visual signals were subjected to a *fluctuating* source of interference which increased with the luminance of the background field; a constant source of interference at each luminance level would produce only a change in the 50 per cent seeing intensity, with no change in the variability of seeing.

It should be stressed that this luminance-dependent variability cannot be ascribed to a fatigue effect of the type reported by Sunga and Enoch (1970) in patients with optic neuritis. At a background luminance of 2.0 log cd m^{-2}, where the difference in threshold variability between patients and controls was most significant, none of the patients showed a fatigue effect either over the course of the experiment or within the groups of ten presentations.

Since there is no firm evidence for the existence of a retinal effect in MS, the likely site for the occurrence of the fluctuating interference is the demyelinated visual pathway. Two possible physiological mechanisms underlying the variable effect reported here are intermittent conduction block and cross-excitation between affected nerve fibres. In the normal vertebrate visual system, the form of the response of a retinal ganglion cell, in terms of its firing rate as a function of time, varies with the intensity of both the stimulus flash and the adapting background (Stone and Fabian, 1968; Enroth-Cugell and Pinto, 1972*a*, *b*; Enroth-Cugell and Shapley, 1973). In particular, the impulse frequency of the initial or final components of the response increases with adaptation level. The capacity of a nerve to transmit high frequency impulses is known to be impaired by demyelination (McDonald and Sears, 1970), and intermittent conduction block has been shown to occur at frequencies which are sufficiently low that they overlap with those occurring in the response of the fibre to natural stimulation (Rasminsky and Sears, 1972). Increased variability in seeing with increase in background luminance could therefore arise as a direct consequence of the increasing vulnerability of the stimulus response signal to intermittent conduction block at the site of a demyelinating lesion.

In addition to intermittent conduction block, we also suggest the possible relevance of interference with signal transmission by cross-excitation between nerve fibres at the demyelinating lesion. Osterman and Westerberg (1975) have postulated that ephaptic transmission between adjacent sensory and motor fibres underlies various paroxysmal phenomena in MS, such as tonic seizures, spinal sensory motor seizures, paroxysmal dysarthria and ataxia, and Lhermitte's sign. Although there is no direct evidence for such side-to-side transmission in man, there is evidence for cross-excitation in congenitally dysmyelinated roots in the dystrophic mouse (Huizar, Kuno and Miyata, 1975; Rasminsky, 1978).

If side-to-side transmission were to occur between nerve fibres in the visual pathway, then interference could arise between fibres signalling the response to the stimulus flash and fibres carrying information concerning background luminance (Barlow and Levick, 1969; Stone and Fukuda, 1974). As activity in the latter fibres increases with the luminance level, interference with signal transmission would also increase. The fluctuating nature of this proposed interference could originate either in the 'luminance' fibres or in the side-to-side transmission process.

If abnormal threshold variability of the kind reported here were present at many retinal sites in a patient's eye, it would be expected to produce a disturbance of everyday vision in bright lights but not in dim ones. One of our patients volunteered this symptom and found that his vision in strong sunlight was much improved by tinted spectacles. We have observed this effect previously in a number of our patients with demyelinating optic neuropathy and McDonald (1977) considers that approximately half the patients with acute optic neuritis notice that they see more clearly in a dimly lit environment than in bright sunlight. In 1926, Percival mentioned obscuration of vision in bright lights as a symptom of acute retrobulbar neuritis and also commented that patients with chronic retrobulbar neuritis saw better in dim light. Lillie (1934) reported a similar symptom in chronic optic neuritis and more recently, Perkin and Rose (1976) in a review of Uhthoff's syndrome, noted increased illumination as a cause of transient visual blurring in some patients with optic neuritis and MS.

Increased variability in seeing may also explain a phenomenon found on tangent screen examination of the visual field in some patients with MS for whom the test object appears to flicker on and off in some areas of the visual field (Frisén and Hoyt, 1974). This occurs most commonly between 10 and 25 degrees eccentricity where, because the test object is normally not greatly above threshold, any increase in threshold variability would result in the object being seen intermittently, that is, appearing to flicker on and off.

SUMMARY

Visual thresholds were measured at four different background luminance levels in patients with multiple sclerosis (MS) and in control subjects by means of frequency-of-seeing curves. Results were examined by probit analysis and measures of threshold and threshold variability were obtained. Comparison of patient and control groups showed that the patient's threshold was significantly raised only at the highest background luminance level, but that threshold variability was greater at all three non-zero background luminance levels tested. In addition, threshold variability increased with background luminance in the MS patients but not in the control subjects. Possible underlying pathophysiological mechanisms are discussed, and it is suggested that this luminance-dependent variability in visual threshold shown by patients with multiple sclerosis may be due to intermittent conduction block or ephaptic transmission occurring within the demyelinated visual pathway.

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CHRONIC MIGRAINOUS NEURALGIA

A VARIANT OF CLUSTER HEADACHE

by J. M. S. PEARCE

(*From the Department of Neurology and Headache Clinic, Hull Royal Infirmary, Hull HU3 2JZ*)

INTRODUCTION

CLUSTER headache (periodic migrainous neuralgia) is a condition which is remarkable in many ways, not least for the galaxy of appellations, eponyms and synonyms which it has attracted. Many authorities have rightly commented on the distinctive and stereotyped symptoms which are usually sufficient in themselves to separate the syndrome from migraine, trigeminal neuralgia and other facial pains.

The classical syndrome has been described in detail by Harris (1926); Horton, MacLean and Craig (1939); Kunkle, Pfeiffer, Wilhoit and Hamrick (1952); Symonds (1956); Bickerstaff (1959); Lance and Anthony (1968); Ekbom (1970); Pearce (1975). Classically, the pain is severe, unilateral, sited mainly around the orbit and temple lasting for 30 to 120 minutes. It is commonly associated with redness and lachrymation, blockage in the nostril and it occurs one to three times daily, frequently at night, for a period of six to twelve weeks. The name cluster headache reflects the tendency for the pain to appear in repeated frequent bouts separated by intervals of complete remission. This latter feature was emphasized by Kunkle *et al.* (1952), and is one of the most characteristic features of the syndrome from which the term cluster headache was properly derived.

Since cluster headache is one of the most important diagnoses in patients attending neurological headache clinics, it is surprising that despite wide publication in both general and specialized journals the correct diagnosis is seldom made on referral. Balla and Walton (1964) noted that the average length of time for the diagnosis to be made was 6.5 years from the first attack, and only one patient in their series of 28 had been correctly diagnosed at the time of referral. Subsequent papers and the present study give no indication of any improved rate of diagnostic accuracy.

This paper attempts to describe a variant of the syndrome which, although sporadically referred to in the literature from North America, Scandinavia and Australia, has not acquired adequate recognition in the United Kingdom: the variant is chronic migrainous neuralgia. Evidence for this assertion is that it has received scant attention in much of the English literature in recent years (Symonds, 1956; Bickerstaff, 1959; Balla and Walton, 1964; Pearce, 1975; Walton, 1977). It differs not only in the clinical pattern of symptoms but also in its treatment.

MATERIAL AND METHODS

The data is derived from the records of hospital and private patients referred over the period June 1967 to January 1979. Clinical details of the history and examination were personally obtained in all patients and were supplemented by selected laboratory tests and radiology when necessary.

RESULTS

Table 1 shows a summary of the sex and age at onset of 95 patients. Peak decades were 20 to 29 years, 30 to 39 years. Seventy (73.7 per cent) of the series commenced their attacks between the ages of 20 and 50 years. Only seven patients (7.4 per cent) were female. In accordance with the criteria of Ekbom (1970), patients were classified as the 'upper syndrome'— 69 patients, or 'lower syndrome' —26 patients. The clinical features of these two groups (Table 2) are characteristic.

The 'upper syndrome' is characterized by pain mainly centred in the eye, forehead and temple, sometimes spreading to the vertex and even the back of the neck.

TABLE 1. PERIODIC MIGRAINOUS NEURALGIA. SEX DISTRIBUTION AND AGE AT ONSET

Age at onset (years)	*10–19*	*20–29*	*30–39*	*40–49*	*50–59*	*60+*
Males	10	24	27	13	8	6
Females	0	2	3	1	1	0
Total	10	26	30	14	9	6

The 'lower syndrome' tends to have a later age of onset, a higher incidence of peptic ulceration and attacks of pain in the cheek and jaw with a partial Horner's syndrome characterized by hyperhidrosis of the ipsilateral forehead.

This separation into the upper and lower syndromes is an arbitrary one which serves some purpose of clinical convenience. It is clear that the separation at this stage appears to have no fundamental significance, but this divisiốn is made so that the present material can be compared with the large series of Ekbom (1970).

The age pattern, clinical and associated features of the whole group are shown in Tables 1 and 2 to indicate that the series as a whole conforms closely to previous descriptions. The incidence of the chronic type of migrainous neuralgia in this study is 6 out of 101 (6.0 per cent).

TABLE 2. CLINICAL FEATURES OF UPPER AND LOWER VARIETIES OF CLUSTER HEADACHE

	Upper syndrome		*Lower syndrome*	
	No.	*%*	*No.*	*%*
Pain				
Boring	40	57	9	35
Burning	23	33	14	54
Dull	1	1.4	0	0
Throbbing	5	8.6	3	11
Site				
Periorbital	69	100	12	46
Malar	18	27	21	80
Upper jaw	2	3	23	89
Lower jaw	0	0	8	31
Neck	0	0	9	35
Associated symptoms				
Red watering eye	59	85	23	89
Nasal congestion	24	35	9	35
Photophobia	41	59	14	54
Phonophobia	32	46	11	42
Vomiting	1	1	0	0
Horner's Syndrome	12	17	7	27
Family history of migraine	23	33	8	15
Past history of migraine	11	16	3	12
Attack rate	0.3–4.0		0.5–3.0	
(Clusters per year)	(Mean 1.2)		(Mean 1.4)	
Total No. Patients	69		26	

Patients in whom a cluster had not ended after sixteen weeks were designated chronic migrainous neuralgia, and Table 3 shows the symptoms and signs in this group.

To illustrate the clinical features of chronic migrainous neuralgia case reports are described.

Case 1

G.M., a 57-year-old ship repairer, presented with four months left sided supraorbital headaches in March 1978. They radiated to the forehead and vertex, being an extremely severe bursting pain. They occurred regularly thirty minutes after a nap in a chair in the evening, or between midnight and 2.00 a.m., usually sixty minutes after falling asleep. There were no visual symptoms or sickness, and he observed no redness or watering of the eye. Attacks occurred four or five days each week and were initially relieved by suppositories of Cafergot on retiring, but this initial benefit diminished and he was unable to work for many months.

There was no previous or family history of note. His general health was good and examination showed no physical signs, blood pressure 170/100, urinanalysis normal. In August 1978 the attacks had continued unabated for nine months.

TABLE 3. CHARACTERISTICS OF CHRONIC MIGRAINOUS NEURALGIA

Patient	*Age (yrs)*	*Sex*	*Duration of total history*	*Duration of chronic cluster*	*Primary or secondary**	*Response to***		
						Ergot	*Methysergide*	*Lithium*
G.M.	57	M	16 mnths	16 mnths	Primary	+	++	+++
C.M.S.	33	F	9 yrs	8 mnths	Secondary	+	+	+++
K.B.	60	M	4½ yrs	3 yrs	Secondary	+	++	+++
E.E.	63	M	2½ yrs	2½ yrs	Primary	++	++	Not used. Abolished by cimetidine
J.R.R.	54	M	4 yrs	8 mnths	Secondary	+	++	Not used
I.A.	60	F	13 yrs	4½ yrs	Secondary	Nil	+++	Not used

* Primary = continuous symptoms from onset. Secondary = initial periods of cluster, followed by continuous attacks.
** Response: +++ = more than 90% reduction of headaches, ++ = 60 to 90% reduction, + = 25 to 59% reduction.

Methysergide was started and almost completely abolished his attacks in a maintenance dose of 3 to 4 mg per day. When he omitted this treatment nocturnal attacks at 3.00 and 4.00 a.m. returned the next day. In accordance with our practice not to give methysergide for longer than four months at a time, the drug was withdrawn in February 1979 with prompt relapse of his symptoms. Lithium carbonate (Camcolit 250 Norgine) 250 mg t.d.s. was substituted and immediately prevented his attacks. He remains symptom-free with no side effects on this regime, to date, having had cluster headache without spontaneous remission for sixteen months.

Case 2

C.M.S., a 33-year-old woman, presented in June 1977 with a history of four bouts of headaches lasting for three to four months during the previous six years. The pain was boring, deep and exceedingly severe. It started in the left upper jaw and spread over the malar region, eye and over the whole of the left side of the head. During attacks the left eye had frequently been seen to be red and bloodshot. Her attacks occurred from twice up to five times in each day, many being nocturnal and lasted for sixty to ninety minutes. In several attacks she vomited, but she never had any visual or sensory symptoms.

Examination showed a large woman, height 71 in (180 cm) weight 210 lbs (95 kg) with no abnormal physical signs, blood pressure 160/90. Radiographs of chest and skull were normal.

A further cluster began in July 1978 and was partly relieved by oral ergotamine, given in anticipation of her attacks. Control was incomplete and she was therefore given methysergide 3 to 6 mg daily in addition to oral ergotamine. This reduced the number of attacks to about a half, but in December, after five months, the cluster had not ended and symptomatic control, though substantial, was not complete.

Lithium carbonate 250 mg b.d. was begun, and increased to 250 mg t.d.s. Blood levels were low (0.28 mmol/l) but her attacks were very mild and infrequent, and finally ended in March 1979—after eight months.

Case 3

K.B. This 60-year-old man, a printer, first attended the clinic in May 1976. He gave an eighteen-month story of periodic right-sided headaches, initially lasting eight weeks, then followed by an eight-month total remission. The symptoms recommenced in March 1976 with pain in the right maxilla of great severity, spreading to the right malar region, temple and orbit. It appeared in alarm clock fashion at 4.00 p.m., 8.00 p.m. and 1.00 a.m., lasting two to three hours feeling like 'severe toothache with stabs of unbearable severity'. In the attacks the right eye was bloodshot and watered and the right nostril poured. Some relief was obtained from a 'red hot water bottle' and ergotamine suppositories, but not tablets, had provided partial relief.

He was given methysergide 1 mg q.d.s. with good relief, but each time it was reduced the pain recurred. In 1977 he developed typical duodenal ulcer symptoms confirmed at a barium meal. In July 1978 he was admitted as an emergency, being considered 'suicidal with pain' by his practitioner. No physical abnormality was found, blood pressure 160/100. Urine analysis, blood urea and excretory urogram were performed because of two years continuous methysergide therapy, but were normal. His pain was controlled with difficulty on a combination of ergotamine suppositories 2 mg eight-hourly and methysergide 2 mg t.d.s.

In September 1978 he reported only six attacks in two months, but still had to continue the same drugs. He had also developed severe generalized weighty, band-like tension headache. A few weeks later this symptom dominated his life and was complicated by bouts of cough headache. He was emotionally disturbed, but his cluster headache was mild and infrequent. Examination and CAT scanning to exclude an incidental subdural hæmatoma were normal. Diazepam failed to improve his headaches and was replaced by amitryptilene. He remained miserable with cough headache but quite distinct brief episodes of cluster headache every three or four days. In October 1978 he was given lithium carbonate 250 mg t.d.s. His serum lithium was maintained at 0.42 mmol/l. His migrainous neuralgia almost completely disappeared, but he remained tense, depressed and was still subject to bouts of tension headache. He had had uninterrupted migrainous neuralgia for three years after a typically periodic pattern for eighteen months.

Case 4

E.E. This 63-year-old fish filleter presented in September 1976 with a six-month history of severe left orbital headaches. A bloodshot appearance in the left eye was observed during his attacks which occurred in alarm clock fashion at 4.00 a.m., 2.00 p.m. and 7.00 p.m. each day, lasting for two to three hours. He had a past history of 'polioencephalitis' twenty years earlier. There were no abnormal signs but he was hypertensive 160/120 mm Hg. Treatment with oral ergotamine 1 mg t.d.s. before the expected attacks was started and methyldopa was given for his hypertension.

This regime controlled his headaches well at first but the benefit wore off and the attacks continued without remission into May 1977. Methysergide was then prescribed 3 to 4 mg daily and afforded considerable relief, but if the drug was omitted, further attacks recurred within twenty-four hours. After four month's treatment it was stopped to prevent toxicity and he then had two to three attacks per week during the autumn of 1977, and was taking analgesics, a large dose of methyldopa 500 mg t.d.s. (blood pressure 210/125). Methysergide was recommenced in March 1978 after a six-month interval and again provided satisfactory relief, although the attacks recurred if tablets were forgotten.

His symptoms became worse after two months on methysergide 2 mg b.d., and he was admitted to hospital for control after twenty-seven months of 'cluster headache', without remission. Attacks were noted regularly at 4.00 a.m., 2.00 p.m. and 6.30 p.m., still in the left eye with marked injection of the conjunctiva and blockage of the left nostril. The methysergide was stopped. A trial of cimetidine 400 mg b.d. in September 1978 instantly abolished his attacks. After six weeks the dose was reduced to 400 mg *nocte* and he had had no further attacks when last seen in January 1979, when he had reduced the cimetidine to three nights each week. Whether the remission was spontaneous after three years of controlled but continuous frequent attacks, or was induced by cimetidine, remains speculative.

Case 5

J.R.R. This 54-year-old farmer sought attention in November 1975. He gave a four-year history of headaches occurring in bouts lasting four to eight weeks. Attacks were precipitated by alcohol, even in small amounts, and also by the bright light of his television set. He complained of right temporal headache of great severity, aching in quality and accompanied by watering and redness of the right eye, blockage of the right nostril and partial closure of the eyelid. He noted bright light aggravated the attack, and the application of cold water or walking outdoors in the cold night air would relieve his pain to some extent. Attacks troubled him one to three times each day; many wakening him from sleep, others occurring at 8.00 p.m. and 3.15 p.m. Apart from these attacks he also had periodic tension headache with the sensation of a tight hat pressed onto his head. He suffered from mild angina but could walk four miles without distress. He took vitamin C, 4 gm daily 'for sinusitis'.

Examination showed a right Horner's syndrome which was present in and between attacks. No other physical signs were present; blood pressure 140/85, urinanalysis was normal.

He was advised to abstain from alcohol and to take ergotamine as a suppository one hour before each anticipated attack. With some difficulty he managed to obtain partial and acceptable control, but he took additional ergotamine orally prescribed by his general practitioner, as well as Diazepam and aspirin for tension headache. This cluster lasted eight months till July, 1976 and he was then free of attacks and without treatment. The next cluster started after only four months freedom. It lasted without remission for eight months, and during this period he took 6 to 10 mg ergotamine daily. Methysergide was added in January 1977 with some effect. He could go a fortnight without nocturnal attacks, but continued to take Migril (Wellcome) at noon and an ergotamine suppository at 7.30 p.m. of his own volition.

He has had subsequent typical clusters for six to eight weeks, usually brought about by alcohol, but quickly and immediately suppressed by methysergide. He takes 2 mg q.d.s., and obtains almost total relief in three days, when he decreases the dose down to a smaller maintenance level of 2 to 4 mg daily for the duration of the cluster. Ergotamine is now rarely used. He has had no vascular complications, and his angina is clinically unchanged.

Case 6

I.A. This 60-year-old woman presented in June 1978. She had a past history of asthma, a duodenal ulcer in 1965 and a right mastectomy for carcinoma in 1977, with an axillary recurrence in January 1978.

Her first headache lasted in short bouts of an hour at a time for a period of one month when she was given carbenoxolone for her duodenal ulcer in 1965. They returned in 1975 and had been present without remission ever since. They occurred almost every day, waking her an hour after going to sleep. She was so frightened of this, that she had taken to going to bed at 1.00 a.m., but this only served to delay her pain for two hours. She described a beating pulsating pain over the right forehead and temple, radiating to the cheek and jaw. She found some minor relief by sitting propped up to an almost vertical posture in bed, but would usually have to go downstairs and there would pace the floor till the headache subsided in one to two hours. She was often reduced to tears. There was mild distaste for the light in attacks, but no teichopsia or vomiting. On occasions her husband would observe redness of the right eye and drooping of the upper lid, but these were inconstant features. She had irregular daytime attacks of less severity.

Examination showed no neurological signs. There were no physical signs of further recurrence of her breast carcinoma. The blood pressure was elevated 200/115, but subsequently dropped to 150/90 mm Hg without treatment.

Before the initial consultation she had seen a physician who had performed a temporal artery biopsy which was normal; he had prescribed ACTH which had controlled her symptoms effectively for six months. All manner of analgesics and sedatives had failed to relieve her, and she had eventually been given methysergide which had provided substantial control, though when the dose was dropped below 3 mg daily, her suffering was renewed. She had been on this drug for six months when first seen by the author, and fearful of long-term toxicity, it was stopped and replaced by pizotifen 1 mg t.d.s. This was used for two months and was ineffective. She was admitted to hospital, by which time her symptoms had abruptly switched to the left side and she was having several brief daytime pain; she took dihydrocodeine and Doloxene with slight relief.

Investigations were undertaken, largely to exclude cranial or cerebral metastases. Blood count, biochemical profile, CSF pressure and constituents and a CAT scan were all normal. After a number of unsuccessful therapeutic trials methysergide was restarted. Within three days the pain had disappeared. It was decided that in view of the prognosis of her carcinoma, the risks of long term methysergide were acceptable, and she has continued in a state of freedom from pain to date, but any reduction below 1 mg b.d. brings back her pain. Lithium has not been tried so far, in view of the difficulty in obtaining control in the past and her reluctance to change from her present simple regime from which she suffers no side-effects. The duration of the 'cluster' is now four-and-a-half years.

DISCUSSION

The term chronic cluster headache is unfortunate. It contains a contradiction in terms, and the designation *chronic migrainous neuralgia* is preferred, although it too has shortcomings, in that many would dispute the migrainous basis of the syndrome.

The diagnosis of classical cluster headache depends on the clinical features; but one of the most important criteria is the frequency and periodicity of the attacks. Ekbom (1970) found the frequency of attacks was usually once per day and their duration varied from 30 to 120 minutes. They occur at any time of the day or night, but are more common at night time usually one to two hours after sleep. Half of his patients had noticed attacks occurred punctually at predictable times ('alarm clock headaches'). The periods were usually once or twice a year, often the autumn or spring, and lasted as a rule for one to two months. Ekbom noted that with increasing age some patients noticed increasingly long asymptomatic intervals. In an earlier study (1968) he had noted the provocation of attacks by alcohol and nitroglycerin in susceptible individuals and this is an occasionally useful provocative test. In his series of 105 patients the age of onset, the male preponderance, the character and distribution of headache and the associated features all correlate very closely with those described in the present study. Of the 105 patients described by Ekbom (1970) 5 patients had what he called 'chronic symptoms'. The chronic syndrome was divided into (1) primary chronic and (2) secondary chronic type, the attacks at first being periodical and later changing to the chronic form. We have adopted this useful classification.

As in other series, a Horner's syndrome when present was a valuable diagnostic sign. It occurred in 17 per cent of patients with the upper syndrome and, interestingly, in 27 per cent of those with the lower syndrome. In those with chronic migrainous neuralgia Horner's syndrome was observed in two patients, the numbers being too small to attempt a comparison in the full series. The syndrome was noteworthy by the fact that facial sweating was not impaired when the Horner's syndrome was present, and indeed was reported by patients to be actually increased on the affected side during attacks. This is therefore a partial Horner's syndrome. This arises because the sympathetic fibres are involved in their postsynaptic portion, as occurs in carotid occlusion. The sweat fibres travel along the wall of the external carotid artery and are therefore spared unless this vessel too is involved. The situation is comparable to that seen in Raeder's syndrome where an inflammatory or granulomatous lesion in the middle cranial fossa produces trigeminal pain and oculosympathetic paralysis. Horner's syndrome in migrainous neuralgia and Raeder's syndrome is clinically identical, though the progressing physical signs in the latter syndrome serve to distinguish the two conditions. Tests of the pupil reaction in both instances shows reduced sensitivity to mydriatics such as atropine and cocaine, but 1/1000 adrenaline produces dilation of the pupil, indicating denervation sensitivity of peripheral origin (Nieman and Hurwitz, 1961).

Ekbom's (1970) delineation of the chronic syndrome is often claimed as the original description but in fact Symonds' paper in 1956 entitled 'A particular variety of headache' clearly described a patient with the chronic syndrome. McArdle (1969) described similar features at the British Migraine Symposium, and discussed the role of trigeminal destructive procedures in its treatment. Kudrow (1977) added further cases and reported the value of lithium treatment in prevention of chronic cluster headache. He added that distinguishing features of chronic cluster headaches were: absence of periods of remission; increased headache attack frequency and diminished responsiveness to prophylactic medications such as ergotamine, methysergide or steroids. Mathew (1978) reported 31 patients with cluster headache of whom 17 had chronic cluster headache, 13 being primary cases, 4 being secondary cases with a history of remissions in previous bouts. This apparently high incidence presumably reflects selection of patients.

The chronic syndrome is defined here as cluster headache continuing for periods of longer than four months, and in this series of 101 patients, 6 examples of chronic type of cluster headache have been discovered. This incidence is very similar to Ekbom's 5 out of 105. Two of these were primary with no previous cluster episodes, and 4 were secondary. The numbers of such cases are small but the usual high male incidence is clearly shown, and with the exception of one patient, all were aged over 50 years at presentation. An initial response to ergotamine was found in all but one patient, and 5 out of the 6 showed satisfactory response to methysergide prophylaxis, if not complete abolition of headache. These results confirm the suggestion (Kudrow, 1977) that chronic cluster headache is less responsive to conventional medication, but perhaps the most important reason for this is our reluctance to use courses of methysergide of longer than four months for fear of retroperitoneal fibrosis and related complications. This limits the value of methysergide in a syndrome characterized by its continuation for months or years at a time. The duration of the chronic cluster headache in this small series varied from eight months to four-and-a-half years without interruption, and it is clear that in many of these patients the long-term use of methysergide poses unacceptable risks. In the three patients in whom lithium was tried an extremely good response was obtained with complete abolition of cluster headache, which persisted with continued therapy. The single case of a man in whom cimetidine apparently abolished a chronic cluster headache after two-and-a-half years unremitting pain is of great interest, but this apparently dramatic response is not borne out by controlled observations in the literature, and this form of therapy is not therefore recommended unless other measures have failed. Lithium was not necessary in two patients because adequate control had been obtained by methysergide. In one woman (I.A.) the continued use of methysergide was felt to be permissible because her life expectation was seriously restricted by breast carcinoma with recurrence.

It is clear that the use of lithium advocated by Kudrow (1977, 1978) represents a significant advance in the treatment of this condition. The dose necessary to control symptoms has been of a low order in our limited experience. Blood levels in patients whose symptoms have been controlled have been much less than the normal therapeutic range cited for patients with manic depressive illness. Levels of 0.28 mmol/l and 0.42 mmol/l have been associated with good symptomatic control in this study. We find that a dosage of lithium carbonate 250 mg t.d.s. has been sufficient to keep patients free of symptoms, and at this level side-effects have not been observed in our experience. Mathew (1978) records 9 out of 17 patients with chronic cluster headache showing more than 90 per cent improvement, but 3 of the patients derived no apparent benefit. Mild side-effects, particularly tremor, nervousness and lethargy were noticed in a minority of cases and serum lithium levels in all patients were below 1.2 mmol/l. Kudrow (1978) reported 13 of 15 patients with chronic cluster headache who were improved by lithium; but 3 of these patients were improved by methysergide and 11 by high dose prednisone.

Many of the patients in this series had been previously regarded as suffering from primary psychiatric disorder or to have non-organic headaches, and the importance of recognizing this distinctive variant of the cluster headache syndrome is stressed. The therapeutic response to lithium in resistant cases is emphasized, but this should not be the primary line of treatment. The continued use of ergotamine and then methysergide is advisable in the initial attempt to control chronic cluster headache, and only if these fail or if the duration of the course of methysergide becomes extended should lithium be used. Blood levels should be performed in the first few weeks, but if they remain stable and below or within the therapeutic range (less than 1.2 mmol/l), and symptoms are abolished, frequent blood assays become unnecessary. Patients who respond well to lithium improve in the first week or two. They remain free of attacks as long as the drug is continued or until the 'cluster' spontaneously ends. During treatment rare 'breakthrough' headaches occur if the dose is dropped or if a vasodilator such as alcohol is taken. The mechanism of the actions of lithium (and indeed of methysergide and prednisone) is not known with certainty. Similarities with the manic-depressive state (Kudrow, 1977) appear superficial and unconvincing. It has been postulated (Mathew, 1978) that its action may be related to its demonstrated action in animals on cerebral monoamines, sodium and potassium; an alternative speculation relates to the ability of lithium to depress REM sleep which tends to correlate with nocturnal attacks of cluster headache. It is not yet known how lithium works, but its therapeutic value is welcome in an otherwise refractory condition.

SUMMARY

A series of 101 patients suffering from cluster headache is examined in this paper. Ninety-five of these patients suffered from the periodic form of the disorder and in clinical symptomatology differed little from the many previous reports in the literature. As in other series, the condition was seldom diagnosed when the patient presented to the clinic.

Six patients had a different pattern. In these there was no brief cluster, but rather a continuous period of once- or twice-daily attacks of migrainous neuralgia without apparent spontaneous remission. Both primary and secondary types of chronic migrainous neuralgia are recognized: in the latter instance attacks which were at first periodic later changed to the continuous or chronic form. In these patients the attacks were less responsive to ergotamine and methysergide than are patients with the periodic cluster headache, although individually useful periods of control of symptoms were obtained with these drugs. The use of lithium in three patients provided continuous control when the drug was used in low dosage, and no side-effects were observed.

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NEUROPSYCHOLOGICAL FUNCTIONS IN THE FOLLOW-UP OF TRANSIENT GLOBAL AMNESIA

by A. MAZZUCCHI, G. MORETTI, P. CAFFARRA *and* M. PARMA

(*From the Clinica Neurologica dell' Università di Parma, Italy*)

INTRODUCTION

TRANSIENT global amnesia has been the subject of many clinical investigations (*see* Fischer and Adams, 1958, 1964) and is now a well-established diagnostic concept in current clinical practice. However, most studies have been devoted to the clinical features of the attack (Poser and Ziegler, 1960; Frank, 1976; Patten, 1971; Greenlee, Crampton and Miller, 1975) and the subsequent effects of the acute episode have received far less attention. In the case histories reported in Fischer and Adams' (1958, 1964) classical study, no patient (except for one who had previously shown signs of dementia) complained of any subsequent disturbance either after a single episode or after multiple attacks. No specific attention to subsequent effects is given by Evans (1966) or Shuttleworth, Morris and Hill (1966). Similarly nothing noteworthy was reported by Heathfield, Croft and Swash (1973) in the follow-up examinations of 8 cases with multiple episodes, and of 11 cases with a single episode. Mumenthaler and Rall (1969) observed no abnormality at 'neurological' examinations carried out at intervals after the first episode. Lou (1968) found a memory defect immediately after one episode in one case, and observed its progressive amelioration over the months, but gives no precise indication of what test or tests were used. Fogelholm, Kivalo and Bergstrom (1975) followed up fifteen cases, but only with EEG tests. Steinmetz and Vroom (1972) studied the neuropsychological condition of two patients after multiple episodes, and of one patient after a single episode; they found prevailing verbal IQ deficits in the first two patients, and a mild deficit of physiognomic memory in the latter. Mathew and Meyer (1974) reported follow-up findings for thirteen patients (with transient global amnesia). In 5 cases, after a single episode, the patients complained of memory or mental disturbance, but no formal testing was done. In another 8 patients, who complained of memory disturbances after multiple attacks of transient global amnesia, detailed testing showed memory deficits and, in 2 patients, WAIS deficit in a clinical background of varying degrees of dementia. Moreover, many of the above patients also showed signs of neurological disorders. To summarize, it would seem from the available observations that clinical follow-up conform substantially to two patterns: (a) some patients undergo other amnesic phases and/or neurological symptoms and in the course of time show signs of variable neurological and neuropsychological deterioration, up to a persistent amnesic syndrome or to dementia (Mathew and Meyer, 1974); (b) other patients, who often suffered only one episode, have an apparently uneventful follow-up and are regarded as being normal (at least according to common clinical standards and to the judgement of the patients' relatives).

The aim of the present study has been to investigate more accurately and systematically the clinical conditions of the second group of patients who are regarded as being 'normal' in their follow-ups. More specifically, our aim has been to ascertain whether, in patients who have experienced only one attack and do not complain of any abnormality, the neuropsychological conditions are really normal or turn out to be abnormal if submitted to systematic and formal testing at varying times after the attacks.

PATIENTS AND METHODS

Patients who in the past had been admitted to hospital for an episode of transient global amnesia were recalled and submitted to clinical assessment and examination in order to select those who showed the following characteristics: (a) having complained of only one episode of transient global amnesia of uncontroversial diagnosis (particularly with regard to epilepsy, hypoglycæmia and migraine); (b) no neurological abnormalities at the time of the examination; (c) did not complain of loss of memory or any other mental difficulty; (d) whose work and family life were satisfactory and

TABLE 1. NEUROPSYCHOLOGICAL TESTING APPLIED TO TRANSIENT GLOBAL AMNESIA AND CONTROLS

Wechsler Bellevue Intelligence Scale:	Full Scale IQ
	Verbal IQ
	Performance IQ
	Mental Deterioration Index
Wechsler Memory Scale:	Logic Memory
	Associate Learning
Digits Forward	
Digits Reversal	
Verbal Learning (10 words)	
Verbal Recall (10 words) after 30 min	
Spatial Memory (12 forms)	
Spatial Recall (12 forms) after 30 min	
Maze Learning	
Maze Recall after 30 min	
Block Tapping Test	
Rey Complex Picture Reproduction after 60 min from Copy	
Rhythms	

who were considered 'normal' by relatives and family doctor. On the basis of these criteria 16 patients were selected (*see below*) and submitted to detailed neuropsychological testing aimed at detecting mental deterioration, asymmetrical scores between verbal and performance IQ, selected verbal or visuo-spatial memory deficits, short-term or long-term memory deficits. The following tests were used (Table 1): (a) intelligence test: Wechsler Bellevue Intelligence Scale; (b) memory tests: Logic Memory and Associate Learning of Wechsler Memory Scale; Digit Span Forward and Reversal; Verbal Learning and Recall after 30 min of 12 Forms; Maze Learning and Recall after 30 min; Block Tapping Test; Rey Complex Figure Reproduction after 60 min from Copy; Rhythms.

The average follow-up of the patient was 226 days; ages ranged from 41 to 66 years (mean age 56.85); 9 males and 7 females (Table 2).

TABLE 2. GENERAL CHARACTERISTICS OF TRANSIENT GLOBAL AMNESIA PATIENTS AND CONTROLS

	Patients	*Controls*
N	16	16
Male	9	7
Female	7	9
Mean age (years)	56.86 (41–66)	54 (48–69)
School level +	10	8
„ „ ++	4	8
„ „ +++	2	0
Average follow-up	226 days	—

Sixteen control subjects were submitted to the same battery of neuropsychological tests used for patients. To match patients as far as possible in socio-economic background, age and educational level, control subjects were (i) selected from patients' relatives and departmental staff; (ii) aged from 48 to 69 years; (iii) fairly comparable in educational level to patients, as indicated in Table 1 and Appendix 2; (iv) not affected by any manifestation of neurological disorder.

CASE HISTORIES

Case 1

T.S., a 60-year-old woman, housewife; past medical history negative except for one episode of thrombophlebitis in the right lower limb the month before.

Characteristics of the attack. After sexual intercourse, the woman repeatedly asked the same questions of her husband, without being able to answer questions about what had happened days before. She orientated correctly around the house and recognized her family. The family doctor, who had been called immediately, found that the arterial pressure was 160/90 mm Hg. The episode was over in two hours. The following day she was admitted to hospital. Both the EEG and neurological examination were negative. For two to three days, although able to remember past and present facts correctly, she still complained of a 'confusion in her head'.

Follow-up. The patient resumed her normal way of life as a housewife without any problems. Her family reported that they noticed no personality change during the period following the attack, nor any change in her memory capacity.

Case 2

M.U., a 57-year-old male, manager in an engineering firm; past history negative.

Characteristics of the attack. Upon waking one morning, he felt rather 'strange', so he stayed at home. He remembered that whilst doing his usual gymnastics he felt a bit confused. His wife did not notice anything at first, but later her husband asked her what time it was and, after being told, again asked the same question. After he had asked a third time, his wife looked at him with concern; he was pale and she realized that he was confused when spoken to. He did not remember that the day before had been Christmas Day, that he and his children had been to Mass, that the handbag his wife showed him was his Christmas present to her, nor to whom the cat belonged. After about ten to fifteen minutes he began to remember that he had been to Mass and then, with difficulty, after about thirty minutes, his memory returned to normal (total duration of attack about forty-five minutes). Two days later he was found to have an arterial pressure of 240/120 mm Hg, which had not been noticed previously.

Follow-up. After undergoing antihypertensive therapy, the patient resumed work normally and without any difficulty even from the point of view of memory. His family and family doctor stated that the patient was completely restored to his pre-morbid condition.

Case 3

N.L., a 54-year-old male, heavy smoker and drinker, past history negative.

Characteristics of the attack. After a heavy lunch, he lay down for a short rest. He then called to his wife to prepare his overalls for him, convinced that he had to return to the factory. He did not remember that it was Saturday, nor that during the morning he had been to visit his sister who lived in a nearby village. He recognized his family and correctly found his bearings around the house. He repeatedly said that he must go to the dentist to have a tooth extracted, and that he had to go to work. His wife called the family doctor who admitted the patient to hospital. Here the patient did not know where he was and again maintained that he had to return to work. After about five hours the episode had progressively cleared up. His arterial pressure was about 110/85 mm Hg. An EEG proved negative. Left retrograde brachial arteriography negative.

Follow-up. After the episode the patient, a skilled workman, returned to work without experiencing any difficulty; no similar episodes occurred; now and then he felt a bit 'confused' if he tired himself.

Case 4

B.I., a 62-year-old male, industrial engineer; fifteen days previously he had undergone a surgical operation on the right carotid artery, and was found to be hyperactive after a brief loss of consciousness.

Characteristics of the attack. He had just arrived home after a tiring car journey. He looked at a familiar name (with address and telephone number) but could not remember whose it was. In the mean time he denied ever having bought the washing machine that was delivered to the house (he had bought it the day before), and telephoned his wife to ask if she had bought it. His wife, worried, called the doctor who advised hospital treatment. On admission, the episode was already passing off (total duration of two hours) but the patient still seemed to be confused. His arterial pressure was 155/95 mm Hg. Neurological examination showed slight hypereflexia of the right limbs and a slight deficit on the right side of the face.

Follow-up. The slight neurological signs disappeared and the patient returned to his normal way of life with no further episodes. He stated that he had no memory difficulties, which was confirmed by his wife.

Case 5

B.D., a 54-year-old woman, housewife; past history negative.

Characteristics of the attack. After getting up and having done a few household chores she bent to lift her grandson out of his cot and felt 'very light-headed and confused', after which she could remember nothing more. Her daughter stated that her mother came downstairs and continually asked what was happening and then burst into tears because she did not know where she was; her mother repeatedly asked the same questions about the running of the house and her family. She was then taken to the doctor who found that her arterial pressure was 180/100 mm Hg and, worried about her amnesic state, sent her to the Neurological Clinic. She arrived there two hours after the onset of the attack and already showed signs of recovering parts of her memory capacity. She fell asleep and upon waking was completely recovered except for the presence of a 'sense of confusion' and a slightly diffuse headache, which disappeared the following day. Both the neurological examination and EEG were negative.

Follow-up. No similar episodes occurred; she had a few short incidents of the 'empty head' feeling for two to three months and then had no further after-effects. Her family and the family doctor considered her to be fully recovered.

Case 6

O.P., a 58-year-old male, doctor; for some months had suffered from short periods of dizziness on getting up in the morning.

Characteristics of the attack. Having finished his surgery appointments, he put the chains on his car and went home. His family noticed that he was acting rather oddly because he kept asking where he was and what he had done during the morning. A doctor friend came and recorded an arterial pressure of 145/90 mm Hg; he observed that the patient retained distant memories but did not remember putting the chains on his car and driving home. The patient continued to ask what time it was, why he was in bed, and what his family were doing around him. He could not easily find his way around the house. He fell asleep and on waking seemed normal for about five minutes, but then relapsed into his earlier state. He fell asleep again about 10 o'clock in the evening and in the morning was fully recovered. Total duration of episode about ten hours. He was admitted to our clinic three days later, when the objective examination and EEG were negative; the laboratory tests normal.

Follow-up. For a few days he had some difficulty in remembering where he had put things, writing prescriptions, and concentrating when reading books. He had no further similar episodes and no further difficulties, and returned to his normal way of life.

Case 7

B.M., a 64-year-old woman, housewife; for some years had suffered from nocturnal 'restless-legs' syndrome, and for about ten years had suffered from arterial hypertension.

Characteristics of the attack. Whilst cycling to visit her sister, she increased her speed owing to rain. On arrival, she asked her sister if she could change her wet clothes. She moved correctly around the house but showed signs of abnormal behaviour; she kept asking the same questions, did not know why she had gone to see her sister and was unable to answer queries about what she had done the preceding day. The doctor recorded arterial pressure of about 200 mm Hg and admitted her to hospital. After about two hours the episode was over but the patient was unable to remember what had happened during that day. The neurological examination proved negative; the EEG showed diffuse slowing; the laboratory tests revealed hypercholesterolæmia.

Follow-up. The episode terminated without leaving any after-effects. The patient, her family and the family doctor claimed that she did not feel spells of abnormal memory or other ailments. Occasionally she had a 'giddy' sensation when standing up from lying down.

Case 8

M.T., a 59-year-old male, farmer; past history negative.

Characteristics of the attack. Whilst planting vines one hour after lunching, his wife, who was working beside him, noticed that the replies he gave to questions were incongruous: it was clear that he did not remember relevant facts and happenings in his family life nor of the previous day's work. The wife urged her husband to stop working but he wanted to continue. He showed no signs of being disorientated, recognized his family and carried out his work correctly. The symptoms were over in about three hours. That evening he went to his doctor who, after checking the arterial pressure, advised hypotensive therapy. After about a week the patient came to our clinic. The objective neurological examination was negative, as were the EEG and laboratory tests; arterial pressure was 155/90 mm Hg.

Follow-up. The episode did not recur. Both the patient and his family affirmed that there seemed no change in his memory capacity and behaviour.

Case 9

M.P., a 63-year-old male, skilled workman; he had suffered from arterial hypertension for about fifteen years, and eleven years prior to the episode had an arterial thrombosis in the left retina; was a heavy smoker and drinker.

Characteristics of the attack. In the morning he got up apparently healthy; washed, shaved and drank some coffee, but immediately after asked his wife if he had shaved and if she had given him his coffee. Seeing his wife's perplexity, he told her that he had the feeling of 'going out of his mind' and asked her to call the doctor. Immediately afterwards he began wandering about the house, repeating the same questions, for example, what time it was, and about his family life. The doctor recorded arterial pressure of 200 mm Hg max. and admitted the patient to the neurological department of the hospital. A tendency to fall to the right in Romberg's test showed up clearly in the objective examination; the EEG was negative, as were the laboratory tests. Even in the ward he continued to wander about restlessly, continually asking where he was and why he was there. About six to seven hours after onset the episode came to an end (at about 2 p.m.).

Follow-up. No further episode occurred; arterial pressure remained quite high. According to the patient and his family his behaviour and memory functions were unaltered.

Case 10

P.A., a 46-year-old man, skilled workman; eight years previously he had been admitted to this clinic for headache, and diagnosed as 'muscle-tensive'. For some years he had reported having episodes of dimming of his eyesight, which however lasted for only brief periods.

Characteristics of the attack. At a football match, he had difficulty in distinguishing the two teams on the pitch and had a 'confused feeling in his head'; other than this he did not remember anything. His friends had not noticed anything particularly unusual, except that he did not seem very interested in the game. After the match he was unable to talk about it since he could not remember the game. It would seem, therefore, according to the patient, that the episode lasted about one hour. The following day he came to our clinic as an outpatient; the objective examination was negative; EEG showed some short sequences of theta waves in the two temporal regions; laboratory tests were within normal limits; arterial pressure normal.

Follow-up. The episode has not recurred and the patient has no ailments. Since the neuropsychological examination, carried out twenty days after the first visit to the clinic, the patient had two further check-ups during the following year and been found healthy.

Case 11

B.G., a 41-year-old male, businessman; suffering from cardiac neurosis, being treated with diazepam and lorazepam, had undergone a syncopal episode, with negative EEG, the year before.

Characteristics of the attack. He went to the stadium with friends one Sunday, after a heavy meal. His friends did not notice anything wrong, and the patient drove himself home. On arrival he became angry with his mother because the second car was not in the garage; he could not remember that he himself had moved the car the day before. He asked, more than once, what he had eaten for lunch and wanted to know about a family event. His mother was alarmed and called the doctor. After recording an arterial pressure of 135/90 mm Hg, the doctor perceived that the patient remembered nothing of the day's events apart from the first minutes of the football match. The patient was put to bed and slept until late evening, when he got up, wandered about the house and eventually went back to bed; his family thought that he seemed confused. The next morning he appeared to be normal again, but did not recall anything of the day before (total duration of episode about fifteen to twenty hours). During the following days he complained of a slight headache. He was examined as an outpatient at our clinic; neurological examination, EEG, ECG and laboratory tests were all normal.

Follow-up. The patient had no further similar episodes, was in good health and had returned to work. According to his family and family doctor he had no memory deficit.

Case 12

F.I., a 55-year-old woman, housewife; past history negative.

Characteristics of the attack. Whilst riding her moped she had a sensation of being in reverse gear and that she was travelling towards the town instead of towards her home. As there was a private clinic nearby she stopped and asked for help. She felt rather confused. In the clinic, her arterial pressure was apparently normal but the physicians kept her in for a further two hours as she still seemed confused and was unable to remember various things about her personal life. The episode was over within two hours; the patient then insisted on returning home alone, despite not feeling completely recovered and not remembering what had happened. The following day she was examined by a neurologist who found no objective abnormalities. The EEG showed evident theta in the temporal regions.

Follow-up. For about a week after the episode she felt the 'sensation of an empty head' but after that no further symptoms. In the opinion of the patient, and of her husband and the family doctor, her memory functions have returned to normal and she has no problems in leading her usual everyday life. Since the neurological examination the patient has had no subjective abnormalities of memory and no further similar episodes.

Case 13

M.M., a 65-year-old woman, housewife; suffers from diverticulum of the sigmoid colon.

Characteristics of the attack. After having had a barium enema at home, during the following defæcation she felt mental 'confusion', dizziness and sickness. She could not remember what happened afterwards, although her family stated that she wanted to know why they had given her an enema and where she was. The family doctor, who had been called, recorded an arterial pressure of 180/100 mm Hg (usually 140/90) and had her admitted to hospital. During the journey she continually asked what she was doing in the car and where she was being taken. At the hospital she was examined by a neurologist who found only a tendency to retropulsion. During a subsequent ophthalmological examination she lost consciousness for a few seconds and was sick (arterial pressure 80 mm Hg max.). She continued to ask her family why she was in hospital and what had happened. The episode ended in the evening. The patient could not and still cannot remember anything about what happened during that day. The EEG showed theta waves in the two temporal regions; laboratory tests proved negative; the otologist found evidence of bilateral senile deafness.

Follow-up. Pain in the nape of the neck, a sense of confusion, and tiredness lasted for about two weeks after the episode. Memory capacity and behaviour had, on the other hand, been normal in the view of her family and family doctor.

Case 14

B.R., a 52-year-old woman, housewife; past history negative.

Characteristics of the attack. When her moped would not start, she had had to run and push it more than once: from then on she recalled nothing else. It was ascertained that she covered the three kilometres home correctly but on her arrival the family noticed that she kept on repeating the same questions about the meal and about her children, and that she did not answer to the point. The family made her lie down and sent for the doctor, who had her admitted to hospital even though, on his arrival, she was already recovering. She was taken to the neurological department where examination was negative, as were the laboratory tests and arterial pressure.

Follow-up. For two to three days following the episode the patient had a feeling of confusion, after which she returned to normal. Memory capacity stated to be unaltered both by the patient and her family.

Case 15

O.B., a 66-year-old woman, former primary school teacher; past history negative.

Characteristics of the attack. On telephoning her daughter one morning, she was surprised to hear her son-in-law answer although she knew he was at home; she asked him more than once what time it was. Being rather alarmed, her daughter and son-in-law informed her husband and the family doctor. When the latter arrived, they found that she had done various household chores correctly, she recognized everybody, but was obviously unable to remember what she had done during the days before; her arterial pressure was low. When her daughter arrived, the patient was amazed to see her several months pregnant. Every time someone came into the room, she behaved as if they had just arrived even though they had in fact not long left the room. The doctor gave her a sedative, and upon waking the episode was over; the patient was well, but did not remember anything of what had happened. The following day at the surgery she underwent a neurological examination which proved normal; the EEG showed a slight presence of theta waves prevalent in the left anterior sylvian area; laboratory tests were normal.

Follow-up. The patient felt confused and had a feeling of nausea for one further day, and then no further symptoms. Memory capacity was stated as unchanged by the patient, her family and the doctor.

Case 16

T.S., a 55-year-old male, skilled workman; past history negative. It was reported that his mother had had a similar episode when she was about 40 years old.

Characteristics of the attack. The patient had spent the morning hunting, with his head uncovered against the sun. On returning home, a neighbour noticed that he kept repeating the same gestures, and going up and down stairs and into the cellar for no reason. The neighbour asked him if he felt all right, but the patient instead of answering asked her where his wife was (she was in hospital) and what he had just done. Before the neighbour felt the doctor should be called, the episode was over (duration of eight hours). The following day the patient visited the doctor, who found no abnormalities, nor did the neurologist who examined him the day after. The EEG was normal, as were the laboratory tests.

Follow-up. The patient stated that he had been healthy since the episode, with no problems either of memory or at work.

RESULTS

The general results for IQ scales and memory tests, for transient global amnesia patients and controls, are summarized in fig. 1 and Appendices 1 and 2. The IQ results are shown in more detail in Table 3 and the memory scores in Table 4. Statistical results are given in Table 5.

Wechsler Bellevue Intelligence Scores show that (i) controls obtained similar mean scores on Full, Verbal and Performance IQ; (ii) transient global amnesia patients obtained higher mean scores than controls on all scales, and verbal scores

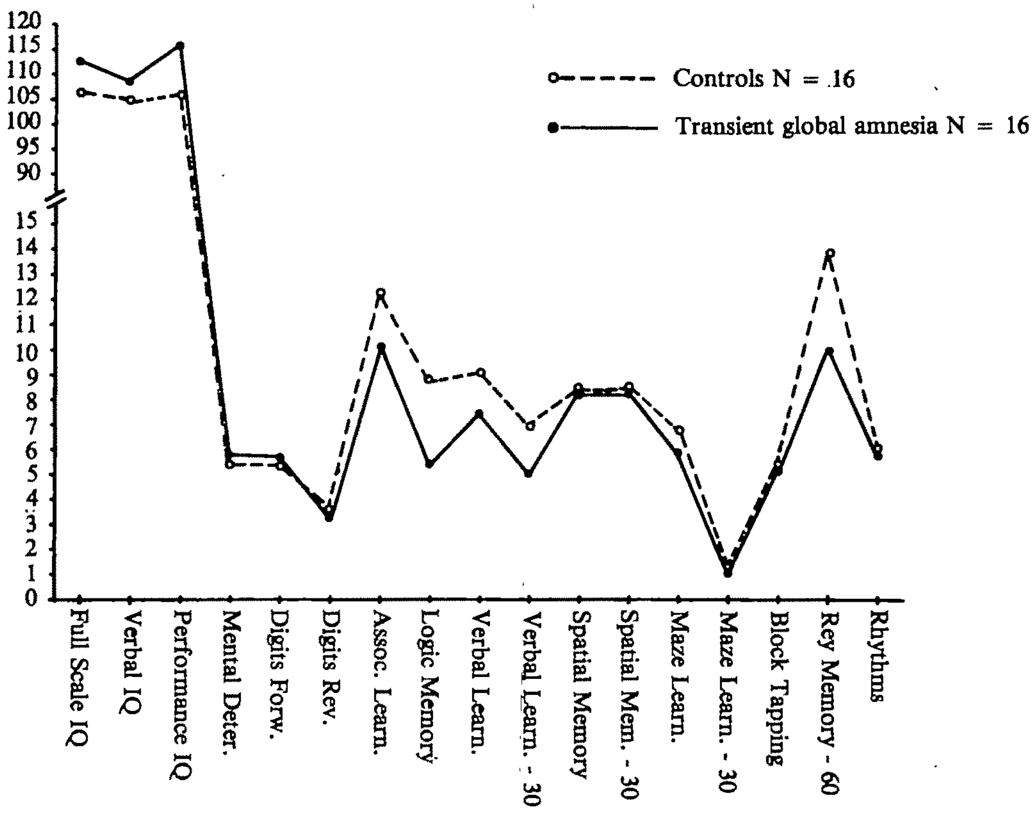

FIG. 1. Mean scores obtained in Wechsler Bellevue Intelligence Scale and in Verbal and Visuo-spatial Memory tests, by patients and controls.

TABLE 3. MEAN SCORES OF WECHSLER-BELLEVUE INTELLIGENCE SCALE IN TRANSIENT GLOBAL AMNESIA PATIENTS AND CONTROLS

Group	*Full IQ*	*Verbal IQ*	*Performance IQ*	*Mental Deterioration*
Controls (N = 16)	Mean 105.87 SD 18.29	Mean 105.25 SD 17.15	Mean 105.40 SD 17.85	Mean 5.43 SD 7.76
Patients (N = 16)	Mean 113.25 SD 15.41	Mean 108.60 SD 15.29	Mean 115.93 SD 15.50	Mean 5.86 SD 8.24

inferior to performance scores (Table 3); (iii) Mental Deterioration index is not significant and is very similar in both groups (mean index 5.86 in patients and 5.43 in controls); (iv) the differences in 'verbal *versus* performance' are not significant in controls, but highly significant in transient global amnesia patients (Table 5).

Individual case analysis (*see* Appendix 1) shows that in 11 cases verbal scale scores are inferior to performance scale scores; in 6 of these cases the differences are very evident (scores marked with asterisks); for the other 5 cases, in one (Case 1) there is no difference between verbal and performance scores, 3 (Cases 2, 9 and 13) show performance scores that are not significantly inferior to verbal scores, and one (Case 1) was not given the WBIS. In one of these patients (Case 11) a significant mental deterioration index was found (Wechsler, 1958).

Memory Test results (Table 4) show that (i) mean scores on tests used to examine short-term, verbal, and visuo-spatial memory are closely similar in patients and

TABLE 4. MEAN SCORES OF MEMORY TESTS IN TRANSIENT GLOBAL AMNESIA PATIENTS AND CONTROLS

	Controls			*Patients*		
Tests	*Mean*		*SD*	*Mean*		*SD*
Digits Forward	5.50	±	0.62	5.75	±	0.79
Digits Reversal	3.61	±	0.51	3.31	±	1.04
Associate Learning	12.31	±	2.52	10.10	±	3.13
Logic Memory	8.96	±	1.63	5.34	±	2.21
Verbal Learning (10 words)	9.12	±	1.20	7.46	±	0.91
Verbal Recall (10 words)—30 min	7.00	±	1.67	5.06	±	1.90
Spatial Memory (12 forms)	7.37	±	1.24	8.37	±	2.40
Spatial Recall (12 forms)—30 min	7.43	±	1.18	8.56	±	2.39
Maze Learning	6.93	±	2.20	5.93	±	1.38
Maze Recall—30 min	1.00	±	0	1.06	±	0.25
Block-tapping test	5.50	±	0.48	5.18	±	0.83
Rey Complex Picture Reproduction—60 min	14.00	±	4.15	10.00	±	3.28
Rhythms	5.87	±	0.61	5.93	±	1.22

controls; (ii) mean scores obtained with visuo-spatial long-term memory are also similar in both groups; (iii) there are significant differences in the mean scores obtained on long-term verbal memory tests and with Rey Complex Figure Reproduction (Table 5). The individual case analysis shows that scores obtained in verbal memory tests (Logic Memory, Associate Learning and Verbal Learning) are defective in almost all patients except the scores indicated by asterisks (Appendix 1).

The levels of statistical significance were calculated for memory tests, IQ Full Scale and mean index of Mental Deterioration by t-test for independent samples (one-tailed) and for IQ differences and 'verbal *versus* performance' by t-test for related samples (two-tailed) calculated separately in patients and controls. The values are shown in Table 5.

TABLE 5. RESULTS OF T-TEST, COMPARING IQ SCORES AND MEMORY TESTS SCORES IN PATIENTS AND CONTROLS

IQ	*t-test*	*P*	*Verbal Memory*	*t-test*	*P*
Full scale	1.27	n.s.	Digits Forwards	1.05	n.s.
Mental Deterioration	1.08	n.s.	Digits Reversal	0.96	n.s.
Verbal *vs* Performance Patients (°)	2.77	< 0.02	Associate Learning	2.33	< 0.05
Verbal *vs* Performance Controls (°)	0.62	n.s.	Logic Memory	4.99	< 0.001
			Verbal Learning (10 words)	4.98	< 0.001
			Verbal Reproduction after 30 min (10 words)	2.81	< 0.01

Spatial Memory	*t-test*	*P*
Block-tapping Test	0.96	n.s.
Rhythms	0.075	n.s.
Spatial Memory	1.29	n.s.
Spatial Recall after 30 min	1.59	n.s.
Maze Learning	1.48	n.s.
Maze Reproduction after 30 min	0.06	n.s.
Rey Complex Picture Reproduction after 60 min from copy	4.33	< 0.001

Levels of statistical significance are calculated with t-test for independent samples (one-tailed) for Memory Tests (verbal and spatial), IQ Full Scale and Mental Deterioration index; and with t-test for related samples (two-tailed) for IQ differences Verbal *vs* Performance (°).

DISCUSSION

The preceding findings seem to lead to the following main conclusions: (a) in contrast to current opinion, accurate testing of transient global amnesia patients who seem to be completely recovered after an episode demonstrates clear abnormalities even if these are not complained of by patients or their families; (b) these abnormalities do not appear to be an expression of diffuse deterioration but rather are selective and conform to a fairly constant and recognizable pattern; (c) the abnormalities are exclusively verbal. More specifically, we have found that the abnormalities concern IQ and long-term memory; the IQ deficits show verbal items to be inferior to performance items. In other words, there is a profile that is the opposite of that found typically in deterioration (physiological, connected with head injury, degenerative CNS illness (Wechsler, 1958; Savage, 1970; Mandleberg and Brooks, 1975)). Not only was no significant index of mental deterioration found but transient global amnesia patients obtained a higher IQ than controls. The higher IQ in our patients was clearly due to a chance factor in selecting patients and controls, but it makes the deficit in the verbal scale more noteworthy. With regard to memory, we found abnormalities of long-term memory only in verbal tests, whereas no abnormalities were found in any of the short-term memory tests or in long-term non-verbal memory tests. The abnormalities found in our cases on the Rey test are not contradictory since this test tends to show a deficit with temporal lobe lesions of either hemisphere. Thus, there is a parallelism between IQ and memory testing: both show prevailing verbal abnormalities. To summarize, the follow-up of 'benign' transient global amnesia cases seems to be characterized by the following syndrome: (a) deficit of verbal IQ; (b) absence of IQ-significant index of mental deterioration; (c) large deficit in long-term verbal memory; (d) no deficit in short-term verbal and non-verbal memory, or in visuo-spatial long-term memory. These data refer to patients as a group compared to controls, but single case analysis also confirms that these findings regarding memory are found individually and in 11 of our cases are verifiable with regard to the IQ pattern.

As stated above, no similar study has been reported in the literature but fragmentary observations can be found which can be compared to ours in some significant respects. For example, in two cases with multiple episodes Steinmetz and Vroom (1972) found a pattern of verbal *versus* performance IQ deficit and impaired Wechsler Verbal Memory scores similar to our findings; in one case with a single attack of transient global amnesia in the medical history, they found a deficit in IQ performance and a deficit in facial recognition testing. They interpreted these results as indicating a left temporal involvement in the first two cases, and a right temporal involvement in the third case. It should however be noted that the facial recognition test is of questionable localizing significance, and this was the only test used. Mathew and Meyer (1974) found deficits in logical memory, in associate learning and in reproduction of figures from memory (Wechsler Memory Test) in all their cases, and in some of their cases there were also deficits in digit span, visuo-spatial and WAIS (particularly in those cases with more deterioration). These findings seem to be partly in agreement with our results (confirming verbal deficit) and partly in disagreement (showing more extensive impairment), but in fact a valid comparative evaluation is not possible since Mathew and Meyer's patients, besides having suffered multiple episodes, showed many signs of neurological involvement and mental deterioration.

The interpretation of the present findings is limited by the purpose and methods of the present research, mainly clinical and descriptive. However, some considerations seem permissible in nosology and anatomo-clinical correlation. With regard to nosology, our studies seem to suggest that the most benign cases of transient global amnesia can no longer be regarded as 'transient' but must be regarded as 'partially transient', and transient global amnesia taken in its general course should be regarded as a nosological entity with two phases: one acute, characterized by the well-known complete syndrome, and one 'chronic', characterized by a more circumscribed but nevertheless constant syndrome. Our findings, however, do not give a definite answer to whether the 'chronic' phase is (a) a simple residual sequela of the acute episode; (b) an autonomous process which begins later, possibly due to the same cause of the acute episode acting more chronically; (c) a pre-existing state suddenly aggravated during the acute state and re-appearing after the acute episode has subsided; or (d) a pre-existing state not correlated in significance, nature or localization to the acute phase. Two points would seem important to note regarding localization of the chronic phase: (i) the prevailing verbal IQ deficit, and (ii) the verbal memory abnormalities. The first finding favours the hypothesis that the process underlying the follow-up syndrome is localized in the left hemisphere. This assumption is permissible since it is now generally accepted that IQ profile with verbal scores inferior to performance is an indicator of left hemisphere involvement, and certainly is no less reliable than the classic formula 'performance inferior to verbal score' that is an indicator of right hemisphere involvement or of global incipient deterioration (Andersen, 1950; Reitan, 1955; Dennerll, 1964; Savage, 1971; Klove, 1974). The second finding, the verbal memory deficit, also seems to indicate a prevailing left hemisphere involvement. This assumption is supported by the well-known observation that right unilateral temporo-hippocampal lesions tend to produce memory deficits not complained of by the patients but demonstrable nevertheless by visuo-spatial tests or by tests not requiring verbal strategies (Kimura, 1963; Milner, 1968; Warrington and James, 1967), and when the left side is involved the deficit is demonstrable by verbal or verbal-like tests (Milner, 1958, 1967, 1970; Milner and Kimura, 1964; Blakemore and Falconer, 1967; Corsi, 1969). This line of argument, emphasizing a left hemisphere involvement, is further confirmed by observations that the well-known classical amnesic syndrome can be due not only to bilateral involvement but also, more rarely, to unilateral left temporal involvement (Walker, 1957; Geschwind and Fusillo, 1966; Benson, Marsden and Meadows, 1974; De Renzi, 1977). All this tends not only to indicate a left hemisphere substratum in a post-transient global amnesia syndrome but may also have implications regarding the substrata of the acute *versus* chronic phase. Thus, the acute phase of transient global amnesia could be seen as the result of the following events: (a) acute bilateral involvement; (b) acute unilateral involvement of the left hemisphere; (c) acute involvement of the right hemisphere which happens to be added to an existing but not clinically manifest lesion on the left side, a possibility shown by Milner with

APPENDIX 1. TRANSIENT GLOBAL AMNESIA

Subjects Age, Sex	Follow-up	School level + Primary ++ Secondary +++ Graduate	IQ		Wechsler Memory		Digits		Verbal Learning		Rey Memory 60 min	Spatial Memory		Maze Learning		Block Tapping	Rhythms
			Full Scale % mental deterioration	Verbal Performance	Logic Memory	Assoc. Learning	Forward	Reverse	Immediate	30 min		Immediate	30 min	Immediate	30 min		
1. T.S. 60 F	1 month	+	n.e.	n.e.	6.5	10	6	3	n.e.	n.e.	13	8	7	n.e.	n.e	5	5
2. M.U. 57 M	11 months	+++	150 0%	142 138	7	9	7	5	9	5	9	7	8	8	1	5	7
3. N.L. 54 M	20 months	+	99.5 3%	98 104	4	5.5	5	3	7	5	5	5	7	8	1	5	5
4. B.I. 62 M	8 months	++	132.3 0%	► 120 139.5	4.5	13	6	3	6	4	10	11	12	6	1	7	5
5. B.D. 54 F	6 months	+	116 10%	113 117	2.5	8.5	6	4	7	0	8	7	6	4	1	4	5
6. O.P. 58 M	12 months	+++	126 8%	► 113 137	7.5	16	6	4	9	8	11	10	10	6	1	6	7
7. B.M. 64 F	1 month	+	111 10%	► 107 116	8.5	12.5	4	3	7	6	13	10	10	7	1	6	6
8. M.T. 59 M	12 months	+	110.5 9%	108 113.5	8	7	5	3	6	5	10	8	9	4	1	4	6
9. M.P 63 M	42 months	++	131.5 0%	117 116	5	10.5	6	4	8	7	11	8	9	6	1	6	6
10. P.A. 46 M	20 days	+	94 0%	94.5 96	3	7	6	3	7	5	8	5	7	6	1	4	6
11. B.G. 41 M	7 days	++	93 30%	94 94	3	9	6	3	8	4	10	4	3	8	1	5	7
12. F.I. 55 F	35 days	+	90 4%	► 86.5 95	2.5	10.5	5	0	8	5	14	10	9	6	1	5	7
13. M.M. 65 F	110 days	+	120 0%	128 125	9	13	6	5	8	7	n.e.	9	9	4	1	6	6
14. B.R. 52 F	6 days	+	100 0%	► 91 113	5	8	5	3	7	7	15	9	8	5	1	5	3
15. O.B. 66 F	18 days	++	121 14%	119 123	7	12	7	4	8	6	7	12	12	5	2	6	8
16. T.S. 55 F	1 month	+	104 0%	► 98 112	3.5	10	6	4	7	3	5	10	11	5	1	6	7

n.e. = not examined.

APPENDIX 2. CONTROLS

Subjects Age, Sex	School Level + Primary ++ Secondary +++ Graduate	IQ			Wechsler Memory		Digits		Verbal Learning		Rey Memory 60 min	Spatial Memory		Maze Learning		Block Tapping	Rhythms
		Full Scale	Verbal	Performance	Logic Memory	Assoc Learning	Forward	Reverse	Immediate	30 min		Immediate	30 min	Immediate	30 min		
1. D.N.V. 53 F	++	96	87	107	8	11	6	3	10	6	15	7	8	7	1	6	6
2. M.M.V. 57 F	++	96	98	96.25	8.5	16	6	3	10	7	14	9	8	9	1	5	6
3. S.B. 49 M	+	115	107	120.75	9	19.5	6	4	10	8	12	10	9	8	1	6	7
4. R.J. 50 F	++	113	111	114	8	12	5	4	10	8	11	5	5	6	1	5	7
5. T.O. 54 F	+	109	111	105	8	15	6	3	10	8	14	7	7	6	1	6	6
6. S.L. 53 M	+	93	96	92.75	8	16	5	4	8	2	8	4	7	6	1	5	6
7. M.A. 55 F	+	109	111	106	11	15	6	3	9	8	14	7	6	5	1	6	6
8. C.R. 53 M	++	104	99	107	10	10	5	4	9	8	17	5	6	9	1	5	6
9. M.A. 63 M	+	107	106	107.75	8	12	5	4	7	9	15	5	5	4	1	5	6
10. B.M. 52 F	+	111	110	113.75	11	12	6	3	7	6	13	9	9	6	1	5	5
11. P.B. 59 M	++	96	99	95.25	8	7	5	4	10	7	14	8	8	14	2	6	5
12. A.A. 69 F	+	122	126	110	8	11	5	3	10	9	16	11	11	6	1	5	6
13. C.A. 48 M	+	96	91	90	7.5	13	6	5	7	6	14	7	6	5	2	5	5
14. B.G. 54 M	++	100	97	102.75	11	15	6	4	9	6	14	9	8	9	1	6	5
15. Z.M. 54 F	++	123	120	109	8.5	11	6	3	10	7	15	7	8	4	1	6	6
16. C.A. 48 F	++	114	114	115.25	13.5	14	6	5	10	7	18	8	8	9	1	6	6

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NEUROCHEMICAL ALTERATIONS IN HUNTINGTON'S CHOREA

A STUDY OF POST-MORTEM BRAIN TISSUE

by E. G. S. SPOKES[1]

(From the MRC Neurochemical Pharmacology Unit, University of Cambridge and the Department of Neurological Surgery and Neurology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ)

INTRODUCTION

HUNTINGTON'S chorea is an autosomal dominant disorder characterized clinically by choreiform movements and progressive dementia (Huntington, 1872), and pathologically by atrophy of the corpus striatum and cerebral cortex (Bruyn, 1968). Although the pathogenesis of the disease is completely unknown, recent advances in neuropharmacology have shed some light on the pathophysiology of choreic movements. In particular, it has been suggested that overactivity in the now well-documented dopaminergic nigrostriatal pathway (Ungerstedt, 1971) may be involved, as drugs which facilitate dopaminergic function, such as L-dopa and d-amphetamine, exacerbate choreic movements (Birkmayer, 1969; Chase, 1973; Klawans and Weiner, 1974) whereas drugs which impede dopaminergic transmission, and are well known to produce iatrogenic parkinsonism, such as α-methyl-para-tyrosine (a competitive inhibitor of tyrosine hydroxylase), tetrabenazine (a central monoamine depletor) and phenothiazines and butyrophenones (post-synaptic dopamine receptor blockers) are useful in ameliorating chorea and are the mainstay of current medical treatment for this condition (Birkmayer, 1969; Chase, 1973; McLellan, Chalmers and Johnson, 1974).

Another means of investigating possible pathophysiological mechanisms in neurological and psychiatric diseases is with biochemical studies on human post-mortem brain tissue. Such studies have revealed abnormalities in neurotransmitters and their biosynthetic enzymes in Parkinson's disease (Ehringer and Hornykiewicz, 1960; Bernheimer, Birkmayer, Hornykiewicz, Jellinger and Seitelberger, 1973; Lloyd and Hornykiewicz, 1970; McGeer and McGeer, 1976), senile dementia (Bowen, Flack, Smith, White and Davison, 1974; Bowen, Smith, White and Davison, 1976; Davies and Maloney, 1976; Perry, Gibson, Blessed, Perry and Tomlinson, 1977), schizophrenia (Bird, Spokes and Iversen, 1979) and Huntington's chorea (Bird and Iversen, 1974; Perry, Hansen and Kloster, 1973;

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[1] Present address: St James' (University) Hospital, Leeds.

McGeer and McGeer, 1976). This experimental approach is valid provided that a standardized system is used for brain collection, dissection and storage, and provided that various ante-mortem factors are taken into account in the interpretation of the biochemical data (Spokes, 1979). From experience gained in our laboratory it has also become evident that there is a considerable individual variation in human post-mortem brain neurochemical values so that large numbers of control and pathological samples must be analysed before firm conclusions can be reached. The influence of ante- and post-mortem factors on the measurements of dopamine, noradrenaline, glutamic acid decarboxylase and choline acetyltransferase in a large control series has recently been reported (Spokes, 1979), and we have presented evidence for increased dopamine concentrations in the nucleus accumbens and anterior perforated substance in brain tissue from schizophrenic subjects (Bird *et al.*, 1979). As an extension of these studies, the biochemical findings in brain tissue from a large series of choreic cases, assayed in parallel with control and schizophrenic material, are reported in the present paper.

CLINICAL DATA

Eighty-three control cases were used in this study (Table 1). In these cases perusal of the available clinical records revealed no history of neurological or psychiatric disease and no patients were known to have received neuroleptic or opiate drugs. However, many patients had been receiving a variety of other medications, in particular thiazide diuretics, antihypertensive agents, digoxin and antibiotics.

TABLE 1. SUMMARY OF CLINICAL AND TISSUE COLLECTION DATA

	Control	*Huntington's chorea*	*Schizophrenia*
Total cases	83	56	59
Age (Mean ± SD) (years)	64.1 ± 19.6	55.5 ± 12.7	59.3 ± 18.9
Age range (years)	18–94	17–77	18–91
Sex: Male	54	29	30
Female	29	27	29
Agonal status			
Sudden death	55	15	23
Protracted terminal illness	28	41	36
Time interval from death to 4° C (h) (Mean ± SD)	2.1 ± 0.9	2.6 ± 1.2	2.9 ± 1.9
Time interval from death to autopsy (h) (Mean ± SD)	42.6 ± 21.2	32.5 ± 19.3	40.0 ± 23.8
Neuroleptic medication	0	46	56
Rigid choreic patients	—	13*	—
Non-rigid choreic patients	—	43**	—

* Of these cases, 6 were receiving dopamine receptor blocking agents, one was receiving these agents plus tetrabenazine, one was receiving tetrabenazine alone and 5 were on no drugs.

** Of these cases, 20 were receiving dopamine receptor blocking agents, 15 were receiving these agents plus tetrabenazine, 3 were receiving tetrabenazine alone and 5 were on no drugs.

Agonal status was considered under two broad categories of sudden death and death following a protracted terminal illness. A more detailed clinical summary of this control series has been reported previously (Spokes, 1979).

Fifty-six cases of Huntington's chorea were used in the study (Table 1). In every instance the clinical diagnosis had been confirmed by neuropathological examinations performed by Professor J. A. N. Corsellis and Dr L. H. Carrasco at Runwell Hospital, Wickford, Essex. Unfortunately, it was not possible to grade the severity of the illness from perusal of the clinical records. Nor was it considered worthwhile to establish the duration of the symptoms, as the disease varies considerably in the rapidity of its course in individual patients. However, a group of 13 patients was identified in whom, late in the disease, chorea had given way to the development of muscular rigidity. In summary, all patients had advanced forms of the illness, had been long-term hospital inpatients, were demented and had shown chorea at some stage of their illness. The majority had been receiving neuroleptic drugs for many years, although a group of 10 patients was identified who had not received such medication for at least six months prior to death. None of the patients had received opiates. All patients had died in hospital, some suddenly, but more after a protracted terminal illness which in every case was bronchopneumonia.

Fifty-nine patients who had died with a hospital diagnosis of schizophrenia were used in the study (Table 1). Of these, 51 had been chronic inpatients before death and all but 3 had been receiving neuroleptic drugs. None had received opiates. Some patients had died suddenly, and others following a protracted terminal illness. This series has already been described (Bird *et al.*, 1979).

Causes of death in all cases, determined at autopsy, as related to the agonal status are as follows:

Controls	SD*	MI (32); accidents (11); RAA (5); PE (4); GIH (3).
	PI**	BP (11); HF (6); MI (5); GIH (3); carcinoma (2); PE (1).
Schizophrenics	SD	MI (15); PE (3); suicide (3); GIH (2).
	PI	BP (20); MI (6); carcinoma (6); HF (4).
Choreics	SD	MI (6); asphyxia (6); PE (3).
	PI	BP (41).

* Sudden death; ** Protracted terminal illness. Clinical abbreviations: MI = myocardial infarction; BP = bronchopneumonia; RAA = ruptured aortic aneurysm; PE = pulmonary embolism; HF = heart failure; GIH = gastrointestinal hæmorrhage.

METHODS

1. *Brain Collection and Handling Procedures*

Brain tissue from all subjects was obtained at autopsy in accordance with criteria described previously (Spokes, 1979; Bird *et al.*, 1979). In the case of specimens from choreic subjects, the brain was divided in the mid-sagittal plane and one half placed in a −20° C deep freeze. The remaining half was fixed by immersion in 10 per cent formalin for histopathological examination. Thereafter, frozen tissue was transported to Cambridge in an insulated box containing dry ice within four days of autopsy. Brains were kept at −20° C for a period no longer than 96 h; more prolonged storage of undissected tissue was carried out at −70° C. The dissection procedure and the anatomical landmarks used to define specific brain areas have been previously reported (Spokes, 1979).

2. *Biochemical Methods*

Frozen brain tissue was homogenized in distilled water (20 per cent w/v) and in most instances aliquots of the same homogenate were taken and treated appropriately for each of the biochemical assays. Dopamine and noradrenaline were measured using 5 per cent homogenates (v/v) in 0.1 N perchloric acid by the radioenzymatic method of Cuello, Hiley and Iversen (1973); glutamic acid decarboxylase (GAD) activity, an enzyme marker for neurons synthesizing GABA, was measured in 20 per cent water homogenates by the radiochemical method of Roberts and Simonsen (1963); choline acetyltransferase (CAT) activity, an enzyme marker for cholinergic neurons, was measured using homogenates of optimum concentration in 0.5 per cent Triton X-100 by the radiochemical method of Fonnum (1969). Total protein was estimated by the method of Lowry, Rosebrough, Farr and Randall (1951) and all values were expressed per unit weight of protein.

Tissues from control, schizophrenic and choreic cases were always assayed in parallel, and all measurements were performed in duplicate. Biochemical measurements were not performed on all areas from all cases, so that the total number of samples reported in the Tables are usually less than the total number of cases used in the study.

RESULTS

Dopamine

In choreic brain tissue, significant increases in the concentration of dopamine were observed in the corpus striatum, pars compacta of the substantia nigra, and the nucleus accumbens; in other regions the concentration of dopamine was

TABLE 2. DOPAMINE LEVELS IN VARIOUS BRAIN REGIONS FROM CONTROL, SCHIZOPHRENIC AND CHOREIC PATIENTS

	Dopamine μg/g protein			*Percentage increase in Huntington's chorea*
Brain region	*Control*	*Schizophrenic*	*Choreic*	
Putamen	23.2±1.1 (77)	22.9±2.2 (37)	39.3±2.2 (56)	69***
Caudate	18.5±0.9 (72)	19.7±1.4 (50)	24.4±1.8 (48)	32**
Lateral pallidum	10.6±0.9 (37)		18.1±1.8 (32)	71***
Medial pallidum	3.8±0.4 (36)		6.8±1.0 (32)	79*
Nucleus accumbens	12.2±1.0 (50)	16.3±1.0 (51)	22.8±1.7 (29)	87***
Substantia nigra Pars compacta	5.0±0.4 (29)		6.7±0.5 (28)	34*
Substantia nigra Pars reticulata	2.6±0.3 (29)		2.9±0.3 (28)	ns
Red nucleus	1.4±0.2 (39)		1.6±0.2 (33)	ns
Anterior perforated substance	1.9±0.3 (33)	3.7±0.6 (37)	2.9±0.7 (16)	ns
Septal nuclei	1.4±0.1 (35)	1.6±0.2 (32)	1.6±0.5 (13)	ns

Values expressed as mean ± SEM. Number of samples in parentheses. $^{*}P < 0.01$; $^{**}P < 0.005$; $^{***}P < 0.001$; ns = not significant, when compared with control values, using Student's t-test.

normal (Table 2). As previously reported, dopamine values were normal in striatal tissue from schizophrenic subjects but significant increases were found in the nucleus accumbens and anterior perforated substance (Bird *et al.*, 1979). The increase in dopamine concentration in the samples of nucleus accumbens from patients with Huntington's chorea was significantly greater than that in the schizophrenic cases. Cumulative frequency distribution curves for individual dopamine values in the putamen and nucleus accumbens from control and choreic subjects are shown in figs. 1A and B. The curves are computed as those expected if the values were normally distributed. The experimental points fitted the computed curves well in all brain regions, as well as those shown in fig. 1, and the results were therefore compared using Student's t-test.

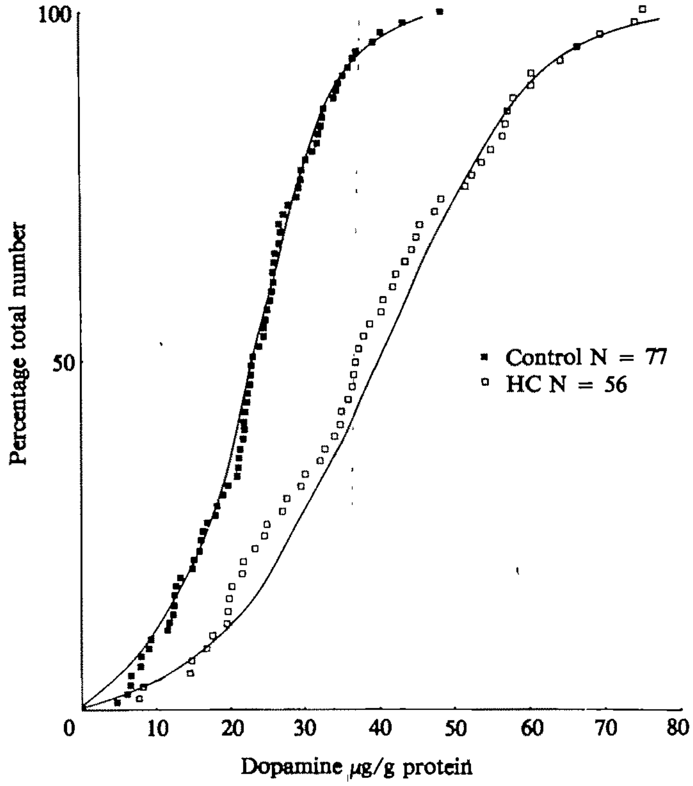

FIG. 1A. Cumulative frequency distribution curves for individual dopamine values in putamen samples from control and Huntington's chorea groups.

When dopamine values in rigid and non-rigid cases of Huntington's chorea were compared, lower levels were found in all brain regions examined in the former group, except the nucleus accumbens, but the differences did not reach statistical

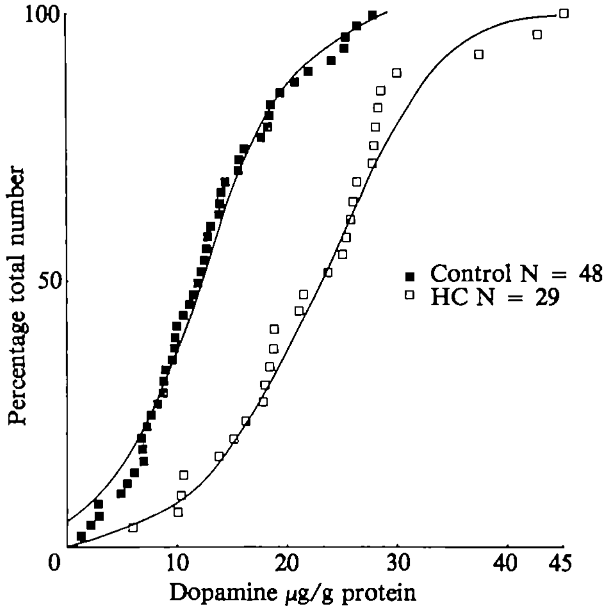

FIG. 1B. Cumulative frequency distribution curves for individual dopamine values in the nucleus accumbens samples from control and Huntington's chorea groups.

TABLE 3. COMPARISON OF DOPAMINE VALUES IN POST-MORTEM BRAIN TISSUE FROM RIGID AND NON-RIGID CHOREIC PATIENTS

	Dopamine μg/g protein	
Brain region	*Rigid*	*Non-rigid*
Caudate	19.9±2.1 (10)	25.7±2.2 (38)
Putamen	36.6±3.7 (13)	40.0±2.7 (43)
Lateral pallidum	14.6±2.1 (6)	18.9±2.1 (26)
Medial pallidum	4.1±0.7 (6)	7.4±1.2 (26)
Substantia nigra Pars compacta	5.3±0.7 (7)	7.2±0.7 (21)
Substantia nigra Pars reticulata	2.0±0.3 (7)	3.2±0.4 (21)
Nucleus accumbens	23.3±2.4 (6)	22.6±1.8 (23)
Red nucleus	1.4±0.4 (7)	1.7±0.3 (26)

Values expressed as mean ±SEM. Number of samples in parentheses. None of the differences between groups was statistically significant.

significance (Table 3); drug treatment did not influence dopamine levels in the choreic cases (Table 4). In both control and choreic groups, highly significant ($P < 0.001$) correlations emerged between dopamine concentrations in the following regions: putamen and caudate; medial and lateral pallidal segments; pars compacta and pars reticulata of the substantia nigra.

TABLE 4. DOPAMINE VALUES IN THE STRIATUM, NUCLEUS ACCUMBENS, SUBSTANTIA NIGRA AND RED NUCLEUS FROM DRUG-TREATED AND DRUG-FREE CHOREIC PATIENTS

	Dopamine µg/g protein	
Brain region	*Drug-treated*	*Drug-free*
Putamen	38.9±2.7 (46)	40.9±4.1 (10)
Caudate	23.9±2.1 (40)	27.1±5.5 (8)
Nucleus accumbens	22.2±2.1 (21)	24.6±3.3 (8)
Substantia nigra Pars compacta	6.9±0.6 (20)	6.2±0.8 (8)
Substantia nigra Pars reticulata	3.0±0.4 (20)	2.6±0.6 (8)
Red nucleus	1.6±0.3 (25)	1.5±0.3 (8)

Values expressed as mean ±SEM. Number of samples in parentheses.

Noradrenaline

In the Huntington's chorea group, significant increases in the tissue noradrenaline concentrations were observed in the caudate nucleus, lateral pallidum, nucleus accumbens and pars reticulata of the substantia nigra, when values were compared using Student's t-test (Table 5); in other regions the concentration of noradrenaline was normal. However, as previously reported (Bird *et al.*, 1979), noradrenaline values did not show a normal statistical distribution in the caudate nucleus, nucleus accumbens and anterior perforated substance in control and schizophrenic subjects, and the same was true for the choreic cases. Application of a non-parametric statistical test (Mann Whitney U test) to compare noradrenaline values in these regions revealed a significant increase in noradrenaline concentrations in the choreic caudate nucleus only. In the control and choreic cases, noradrenaline values were normally distributed in the lateral pallidum and pars reticulata, as revealed by cumulative frequency distribution curves, and could therefore be compared using Student's t-test.

Neither the development of muscle rigidity nor neuroleptic medication was associated with a significant alteration in the measured levels of noradrenaline in choreic brain regions (Tables 6 and 7). In both control and choreic groups there were highly significant correlations ($P < 0.001$) between noradrenaline values in the medial and lateral pallidal segments, and the pars compacta and pars reticulata of the substantia nigra.

TABLE 5. NORADRENALINE LEVELS IN VARIOUS BRAIN REGIONS FROM CONTROL, SCHIZOPHRENIC AND CHOREIC PATIENTS

	Noradrenaline μg/g protein			*Percentage increase in Huntington's chorea*
Brain region	*Control*	*Schizophrenic*	*Choreic*	
Putamen	0.9 ± 0.1 (76)	0.9 ± 0.1 (37)	1.0 ± 0.1 (56)	—
Caudate nucleus	0.8 ± 0.1 (72)	0.7 ± 0.1 (40)	1.3 ± 0.2 (48)	62.5***a*
Lateral pallidum	0.8 ± 0.1 (36)		1.1 ± 0.1 (32)	37.5*
Medial pallidum	1.2 ± 0.1 (35)		1.3 ± 0.1 (32)	—
Nucleus accumbens	1.3 ± 0.1 (40)	1.8 ± 0.2 (47)**c*	1.9 ± 0.3 (29)	46**b*
Substantia nigra Pars compacta	1.3 ± 0.1 (29)		1.5 ± 0.1 (28)	—
Substantia nigra Pars reticulata	1.0 ± 0.1 (29)		1.4 ± 0.1 (28)	40***
Red nucleus	1.7 ± 0.1 (39)		1.7 ± 0.1 (33)	—
Septal nuclei	4.2 ± 0.7 (35)	4.2 ± 0.1 (32)	4.6 ± 0.9 (13)	—
Anterior perforated substance	0.8 ± 0.1 (33)	1.4 ± 0.2 (35)**d*	1.3 ± 0.4 (14)	—

Values expressed as mean ± SEM. Number of samples in parentheses. * $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$, when compared with controls using Student's t-test. *a*, $P = 0.013$; *b*, $P = 0.131$; *c*, $P = 0.129$; *d*, $P = 0.112$, when compared with controls using the Mann Whitney U test.

Glutamic Acid Decarboxylase

In previous studies, we have demonstrated the importance of the agonal status in influencing measurements of GAD activity in control and schizophrenic post-mortem brain (Spokes, 1979; Bird *et al.*, 1979). In control and schizophrenic subjects dying suddenly, GAD activities were similar in all brain regions examined, and reductions in enzyme activity associated with a protracted terminal illness were of the same magnitude in both groups (Table 8). When sudden death choreic cases were compared with sudden death control and schizophrenic cases, there were significant decreases in GAD activity in all regions of choreic grain (Table 8). When data from sudden death and protracted terminal illness choreic cases were compared however, no further loss of GAD activity in the protracted illness group was observed except in the caudate nucleus and putamen (Table 8).

TABLE 6. COMPARISON OF NORADRENALINE VALUES IN VARIOUS BRAIN REGIONS FROM TERMINALLY RIGID AND NON-RIGID CHOREIC PATIENTS

	Noradrenaline μg/g protein	
Brain region	*Rigid*	*Non-rigid*
Putamen	1.2±0.3 (13)	1.0±0.1 (43)
Caudate nucleus	1.2±0.3 (10)	1.3±0.2 (38)
Lateral pallidum	0.7±0.2 (6)	1.2±0.2 (26)
Medial pallidum	0.8±0.3 (6)	1.4±0.2 (26)
Substantia nigra Pars compacta	1.2±0.2 (7)	1.6±0.1 (21)
Substantia nigra Pars reticulata	1.1±0.2 (7)	1.5±0.2 (21)
Nucleus accumbens	2.0±0.7 (6)	1.9±0.3 (23)
Red nucleus	1.4±0.1 (7)	1.8±0.2 (26)

Values expressed as mean ±SEM. Number of samples in parentheses.

TABLE 7. NORADRENALINE VALUES IN VARIOUS BRAIN REGIONS FROM DRUG-TREATED AND DRUG-FREE CHOREIC PATIENTS

	Noradrenaline μg/g protein	
Brain region	*Drug-treated*	*Drug-free*
Putamen	1.0±0.1 (46)	1.1±0.2 (10)
Caudate nucleus	1.3±0.2 (38)	1.0±0.3 (9)
Nucleus accumbens	2.0±0.3 (21)	1.7±0.4 (8)
Substantia nigra Pars compacta	1.6±0.1 (20)	1.4±0.2 (8)
Substantia nigra Pars reticulata	1.4±0.2 (20)	1.3±0.2 (8)
Red nucleus	1.7±0.2 (25)	1.8±0.2 (8)
Septal nuclei	4.7±1.2 (6)	4.5±1.3 (7)

Values expressed as mean ±SEM. Number of samples in parentheses.

TABLE 8. INFLUENCE OF AGONAL STATUS ON GLUTAMIC ACID DECARBOXYLASE (GAD) ACTIVITY IN AUTOPSY BRAIN TISSUE FROM CONTROL, INPATIENT SCHIZOPHRENIC AND CHOREIC PATIENTS

Brain region	*Agonal status*	*GAD μmol/h/g protein*		
		Control	*Schizophrenic*	*Choreic*
Substantia nigra Pars compacta	SD	109.1±10.0 (18)	97.3±12.5 (13)	22.8± 4.8 (8)
	PI	25.7± 7.5 (11)	28.3± 3.6 (12)	29.0± 4.9 (20)
Substantia nigra Pars reticulata	SD	84.2± 9.2 (18)		18.8± 4.0 (8)
	PI	28.8± 7.2 (11)		25.6± 4.3 (20)
Medial pallidum	SD	97.2± 8.1 (22)		30.4± 6.6 (7)
	PI	32.9± 7.1 (14)		28.4± 4.6 (25)
Lateral pallidum	SD	92.9± 8.5 (22)	88.2±11.1 (13)	20.8± 2.7 (7)
	PI	35.0± 8.2 (14)	33.8± 3.3 (12)	19.4± 2.3 (25)
Nucleus accumbens	SD	84.4± 6.3 (36)	80.7± 8.3 (14)	56.6±17.8 (10)
	PI	40.9± 6.3 (15)	48.8± 4.5 (36)	30.3± 3.7 (20)
Putamen	SD	57.9± 3.9 (51)	60.4± 7.3 (13)	21.6± 3.5 (15)
	PI	34.9± 4.5 (24)	34.4± 4.1 (28)	13.8± 2.0 (41)*
Caudate nucleus	SD	48.0± 3.1 (49)	48.7± 6.9 (18)	18.6± 3.8 (13)
	PI	25.9± 3.8 (23)	27.0± 2.8 (33)	11.1± 1.7 (39)*
Dentate nucleus	SD	48.6± 3.0 (24)	36.7± 4.6 (9)	20.9± 2.5 (6)
	PI	23.3± 3.3 (11)	20.0± 4.6 (14)	28.1± 4.7 (23)

		GAD μmol/h/g protein		
Brain region	*Agonal status*	*Control*	*Schizophrenic*	*Choreic*
Cerebellar cortex	SD	32.7 ± 3.2 (20)	34.8 ± 5.7 (5)	16.9 ± 3.0 (7)
	PI	15.2 ± 3.4 (12)	17.1 ± 3.7 (10)	16.1 ± 3.1 (15)
Motor cortex	SD	53.4 ± 3.9 (15)	42.4 ± 7.2 (5)	27.9 ± 3.1 (10)
	PI	22.7 ± 5.5 (9)	22.1 ± 5.5 (9)	21.6 ± 3.1 (17)
Hippocampus	SD	26.2 ± 2.3 (32)	24.2 ± 4.2 (19)	9.4 ± 1.4 (9)
	PI	12.9 ± 1.9 (12)	10.6 ± 1.7 (25)	11.0 ± 1.3 (14)
Anterior perforated	SD	32.5 ± 3.9 (23)	36.1 ± 2.1 (13)	21.8 ± 1.9 (5)
	PI	15.4 ± 2.9 (10)	21.8 ± 2.4 (26)	20.2 ± 3.1 (12)
Olivary nucleus	SD	18.6 ± 2.1 (20)	14.8 ± 2.4 (5)	8.6 ± 1.8 (7)
	PI	6.6 ± 2.7 (10)	5.5 ± 2.1 (12)	9.1 ± 1.9 (21)
Septal nuclei	SD	16.4 ± 2.2 (19)	15.1 ± 2.3 (12)	8.9 ± 3.6 (4)
	PI	8.3 ± 1.4 (9)	7.1 ± 0.9 (20)	9.4 ± 1.7 (9)
Red nucleus	SD	21.4 ± 2.0 (26)		11.3 ± 2.6 (10)
	PI	10.2 ± 2.4 (13)		15.6 ± 1.9 (23)

All values expressed as mean ± SEM. Number of samples in parentheses. SD = Sudden death; PI = Protracted terminal illness. * $P = 0.05$, when compared with sudden death choreic cases, associated with 36 and 40 per cent reduction in GAD activity in the putamen and caudate, respectively.

Regardless of the immediate cause of death, all choreic patients are suffering from a chronic, progressive, physically debilitating disease. Patients in the terminal stages of the illness are usually emaciated and frail and their physical activity is considerably restricted. In this light the distinction between sudden death and protracted terminal illness becomes blurred and it is reasonable to consider Huntington's chorea *per se* as a protracted terminal illness. In contrast, long-term schizophrenic inpatients who die suddenly have generally been physically robust and active prior to death. The GAD activities in the total choreic group (sudden death and protracted illness) were therefore compared with those from control and schizophrenic cases suffering a protracted terminal illness. When the data were handled in this fashion, significant decreases in GAD activity were confined to the caudate nucleus, putamen and lateral pallidal segment (Table 9). If the premises for analysing the data in this way are correct, only in these regions can the reduction in GAD activity be regarded as real.

Cumulative frequency distribution curves for individual GAD values in the putamen from control subjects dying with a protracted terminal illness and from the total choreic group are shown in fig. 2. These data, and those in the caudate and lateral pallidum, showed a normal distribution and were, therefore, compared using Student's t-test. Neither the development of muscle rigidity nor treatment

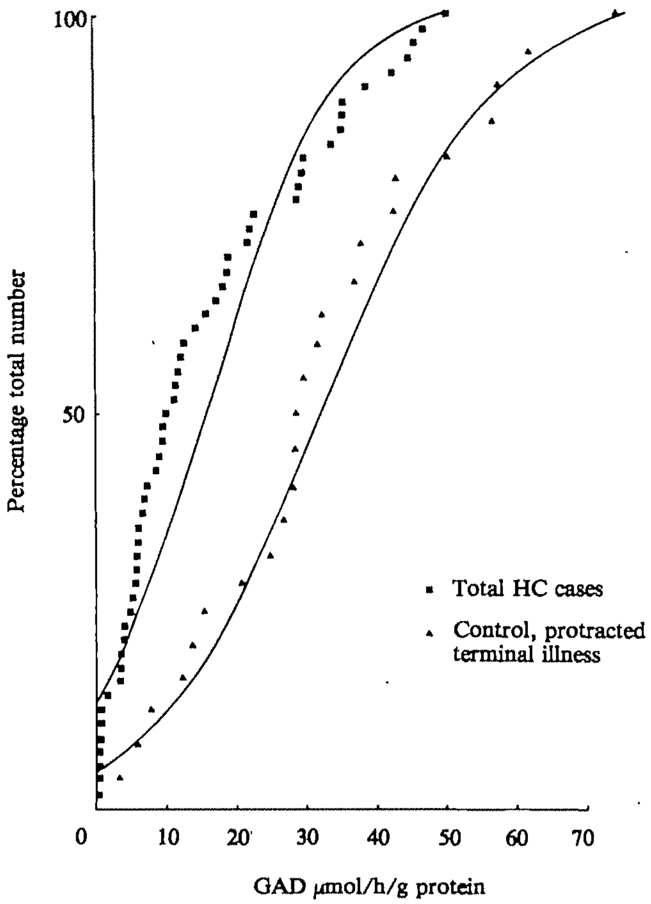

FIG. 2. Cumulative frequency distribution curves for individual GAD values in putamen samples from control subjects dying with a protracted terminal illness and the total choreic group.

TABLE 9. COMPARISON OF GLUTAMIC ACID DECARBOXYLASE (GAD) ACTIVITY IN AUTOPSY BRAIN TISSUE FROM CONTROL AND SCHIZOPHRENIC CASES DYING FROM A PROTRACTED TERMINAL ILLNESS AND ALL CASES OF HUNTINGTON'S CHOREA

	GAD μmol/h/g protein			*Percentage reduction in Huntington's chorea*
Brain region	*Control*	*Schizophrenic*	*Choreic*	
Substantia nigra Pars compacta	25.7±7.5 (11)	28.3±3.6 (12)	27.3±3.6 (28)	—
Substantia nigra Pars reticulata	28.8±7.2 (11)		23.7±3.1 (28)	—
Medial pallidum	32.9±7.1 (14)		28.9±4.5 (32)	—
Lateral pallidum	35.0±8.2 (14)	33.8±3.3 (12)	19.1±2.0 (32)	45*
Putamen	34.9±4.5 (24)	34.4±4.1 (28)	15.9±1.9 (56)	54**
Caudate nucleus	25.9±3.8 (23)	27.0±2.8 (33)	13.0±1.6 (52)	50**
Nucleus accumbens	40.9±6.3 (15)	48.8±4.5 (36)	39.1±6.6 (30)	—
Cerebellar cortex	15.2±3.4 (12)	17.1±3.7 (10)	16.3±2.3 (22)	—
Dentate nucleus	23.3±3.3 (11)	20.0±4.6 (14)	26.5±3.6 (29)	—
Red nucleus	10.2±2.4 (13)		14.3±1.7 (33)	—
Olivary nucleus	6.6±2.7 (10)	5.5±2.1 (12)	9.0±1.5 (28)	—
Motor cortex	22.7±5.5 (9)	22.1±5.5 (9)	23.9±2.3 (27)	—
Hippocampus	12.9±1.9 (12)	10.6±1.7 (25)	10.4±1.1 (23)	—

All values expressed as mean ± SEM. Number of samples in parentheses.
* $P < 0.025$; ** $P < 0.001$, using Student's t-test.

with neuroleptic drugs were associated with a change in GAD activity in various regions of choreic brain (Tables 10 and 11). In both the control and choreic groups, highly significant ($P < 0.001$) correlations existed between GAD activities in the following regions: caudate and putamen; caudate and nucleus accumbens; each pallidal segment and pars compacta; each pallidal segment and pars reticulata; pars compacta and pars reticulata.

TABLE 10. COMPARISON OF GLUTAMIC ACID DECARBOXYLASE (GAD) ACTIVITY IN VARIOUS BRAIN REGIONS FROM TERMINALLY RIGID AND NON-RIGID CHOREIC PATIENTS

	GAD μmol/h/g protein	
Brain region	*Rigid*	*Non-rigid*
Putamen	17.5±4.1 (13)	15.4±2.1 (43)
Caudate nucleus	14.2±4.0 (11)	12.7±1.8 (41)
Lateral pallidum	16.1±4.9 (6)	20.5±2.1 (26)
Medial pallidum	24.0±9.0 (6)	29.9±4.3 (26)
Substantia nigra Pars compacta	29.4±6.1 (7)	26.6±4.4 (21)
Substantia nigra Pars reticulata	24.0±4.6 (7)	23.5±4.2 (21)
Nucleus accumbens	42.9±7.9 (6)	38.1±8.1 (24)
Red nucleus	13.3±3.1 (7)	14.6±1.7 (26)

Values expressed as mean ±SEM. Number of samples in parentheses.

Choline Acetyltransferase

In choreic brain tissue, significant losses of CAT activity were observed in the striatum, nucleus accumbens, septal nuclei and hippocampus (Table 12). Normal values were obtained in all brain regions from schizophrenic cases as reported previously (Bird *et al.*, 1979). Cumulative frequency distribution curves for individual CAT values in the caudate nucleus from control and choreic subjects are shown in fig. 3. In this region, and in the putamen, nucleus accumbens, septal nuclei and hippocampus, the data showed a normal distribution and were, therefore, compared by Student's t-test. The terminal development of muscle rigidity in the choreic subjects was not associated with an alteration in CAT activity in the various brain regions examined (Table 13) and neuroleptic drug treatment did not influence the results (Table 14).

TABLE 11. GLUTAMIC ACID DECARBOXYLASE (GAD) ACTIVITY IN VARIOUS BRAIN REGIONS FROM DRUG-TREATED AND DRUG-FREE CHOREIC PATIENTS

	GAD μmol/h/g protein	
Brain region	*Drug-treated*	*Drug-free*
Putamen	15.6±2.2 (46)	18.8±3.8 (10)
Caudate nucleus	13.5±1.8 (43)	11.2±3.7 (9)
Nucleus accumbens	40.5±9.2 (21)	36.8±5.5 (9)
Substantia nigra Pars compacta	28.3±4.7 (20)	24.7±4.9 (8)
Substantia nigra Pars reticulata	25.1±4.4 (20)	20.1±3.6 (8)
Red nucleus	14.6±1.7 (25)	13.4±3.1 (8)
Dentate nucleus	27.0±4.4 (20)	25.4±4.1 (9)
Motor cortex	24.2±4.0 (20)	23.0±3.7 (7)
Hippocampus	10.2±1.3 (17)	10.9±1.7 (6)

Values expressed as mean ±SEM. Number of samples in parentheses.

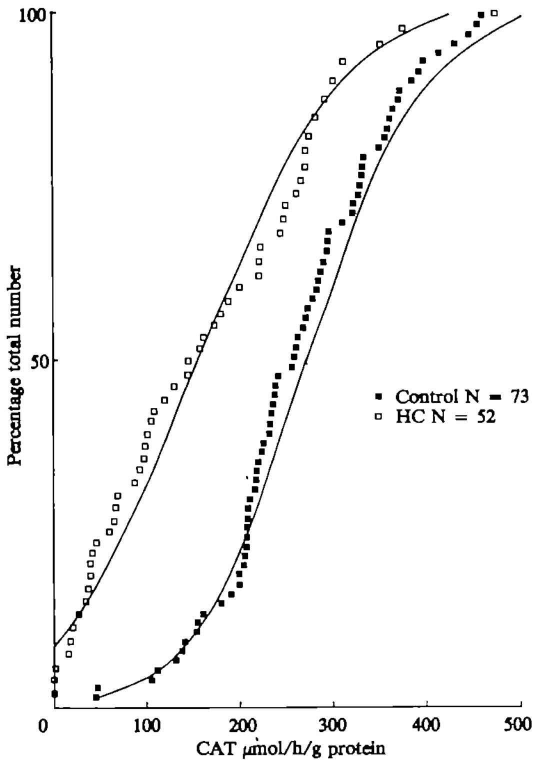

FIG. 3. Cumulative frequency distribution curves for individual CAT values in the caudate nucleus samples from control and Huntington's chorea groups.

TABLE 12. COMPARISON OF CHOLINE ACETYLTRANSFERASE (CAT) ACTIVITY IN VARIOUS BRAIN REGIONS FROM CONTROL, SCHIZOPHRENIC AND CHOREIC PATIENTS

	CAT μmol/h/g protein		
Brain region	*Control*	*Schizophrenic*	*Choreic*
Putamen	346.5±12.0 (76)	308.8±18.5 (41)	226.6±18.5*** (56)
Caudate nucleus	270.9±11.7 (72)	255.5±15.4 (51)	153.8±16.1*** (52)
Nucleus accumbens	226.3±10.6 (50)	198.1±10.7 (48)	186.8±17.1* (30)
Lateral pallidum	49.1± 4.8 (35)		37.4± 5.5 (32)
Medial pallidum	16.2± 3.1 (35)		16.0± 2.0 (32)
Anterior perforated substance	54.6± 8.5 (33)	63.9± 7.6 (37)	60.1±10.9 (17)
Septal nuclei	17.8± 1.7 (28)	18.4± 2.1 (31)	11.2± 1.9* (13)
Hippocampus	13.6± 0.8 (47)	14.7± 1.8 (51)	9.8± 0.6** (23)
Substantia nigra Pars compacta	10.3± 0.9 (29)		9.9± 1.0 (28)
Substantia nigra Pars reticulata	5.2± 0.5 (29)		5.9± 0.7 (28)
Red nucleus	9.3± 0.8 (39)		8.7± 0.9 (33)
Dentate nucleus	4.0± 0.2 (35)	4.2± 0.3 (23)	3.8± 0.3 (27)
Cerebellar cortex	4.6± 0.4 (32)	4.1± 0.8 (15)	3.8± 0.4 (22)
Olive	4.6± 0.4 (29)	4.4± 0.5 (17)	4.0± 0.7 (28)
Motor cortex	5.8± 0.4 (26)	5.6± 0.5 (14)	5.9± 0.4 (27)

Values expressed as mean ±SEM. Number of samples in parentheses. *** $P < 0.001$; ** $P < 0.005$; * $P < 0.05$. Percentage reductions in choreic brain as follows: putamen, 23; caudate nucleus, 43; nucleus accumbens, 17; septal nuclei, 37; hippocampus, 28.

TABLE 13. COMPARISON OF CHOLINE ACETYLTRANSFERASE (CAT) ACTIVITY IN VARIOUS BRAIN REGIONS FROM TERMINALLY RIGID AND NON-RIGID CHOREIC PATIENTS

	CAT μmol/h/g protein	
Brain region	*Rigid*	*Non-rigid*
Putamen	235.0±25.6 (13)	223.8±23.1 (43)
Caudate nucleus	156.4±34.6 (11)	153.1±18.7 (41)
Lateral pallidum	31.8± 9.2 (6)	38.9± 6.4 (26)
Medial pallidum	14.5± 1.2 (6)	16.4± 2.4 (26)
Substantia nigra Pars compacts	11.7± 2.3 (7)	9.3± 1.1 (21)
Substantia nigra Pars reticulata	5.9± 1.3 (7)	5.9± 0.8 (21)
Nucleus accumbens	212.2±29.0 (6)	196.4±25.4 (24)
Red nucleus	8.1± 1.0 (7)	7.7± 1.2 (26)

Values expressed as mean ±SEM. Number of samples in parentheses.

TABLE 14. CHOLINE ACETYLTRANSFERASE (CAT) ACTIVITY IN VARIOUS BRAIN REGIONS FROM DRUG-TREATED AND DRUG-FREE CHOREIC PATIENTS

	CAT μmol/h/g protein	
Brain region	*Drug-treated*	*Drug-free*
Putamen	230.3±22.2 (46)	211.0±33.9 (10)
Caudate nucleus	159.4±17.9 (43)	126.9±39.2 (9)
Nucleus accumbens	206.6±27.6 (21)	183.0±29.4 (9)
Substantia nigra Pars compacta	10.6± 1.3 (20)	8.4± 1.4 (8)
Substantia nigra Pars reticulata	6.3± 0.8 (20)	4.8± 1.0 (8)
Red nucleus	8.7± 1.2 (25)	8.1± 1.2 (8)
Dentate nucleus	3.8± 0.4 (20)	3.7± 0.7 (7)
Motor cortex	5.9± 0.5 (20)	5.9± 0.6 (7)
Hippocampus	9.9± 0.8 (17)	9.5± 1.0 (6)

Values expressed as mean ±SEM. Number of samples in parentheses.

Highly significant ($P < 0.001$) correlations in CAT activities emerged in both control and choreic groups in the following brain regions: putamen and caudate; lateral and medial pallidal segments; nucleus accumbens and caudate; septal nuclei and hippocampus.

Protein

In all brain regions examined, no significant differences were observed for protein concentrations of the tissue homogenates when control, schizophrenic and Huntington's chorea groups were compared.

DISCUSSION

Neurochemical abnormalities in brain regions affected by the pathological changes of Huntington's chorea might arise from a variety of mechanisms so that both increases and decreases in the levels of neurochemical substances are possible. If neurons intrinsic to a particular brain region degenerate, decreases might be expected in the concentration of neurotransmitters elaborated by such cells and in the activities of their respective synthetic enzymes when the region is biochemically analysed. However, the apparent loss of neurotransmitter or enzyme activity will depend upon the balance of cell death and tissue shrinkage. Thus if these processes are in equilibrium, with the effect that the density of remaining normal cells is unaltered, no changes will be evident per unit weight of tissue although the net content of neurotransmitter or enzyme may be considerably reduced. Death of cells which normally project efferent fibres to brain areas extrinsic to the pathological region might be expected to produce a depletion in the levels of neurotransmitters and their related enzymes in the target sites of such fibres. Conversely, a brain region undergoing atrophy might show increases in the levels of neurotransmitters and enzymes contained within intact afferent fibres to the region, as tissue shrinkage might produce an increased density of such fibres.

In addition to these possible anatomical explanations for biochemical changes in diseased brain tissue, it is also important to consider the possibility of adaptive changes occurring in persisting cells, arising through the operation of feedback mechanisms, which might influence the levels of neurotransmitters and the activities of their synthetic enzymes. The presumed neurotransmitter pathways pertinent to the present study are outlined in fig. 4.

There are two major dopaminergic systems in mammalian brain: the nigrostriatal pathway, arising from pigmented cell bodies in the pars compacta of the substantia nigra and projecting rostrally to the corpus striatum (Ungerstedt, 1971) (fig. 4); and the mesolimbic pathway, arising from pigmented cell bodies in the region of the interpeduncular nucleus of the midbrain and ascending to various limbic areas which include the nucleus accumbens lying rostroventrally in the striatal complex (Ungerstedt, 1971).

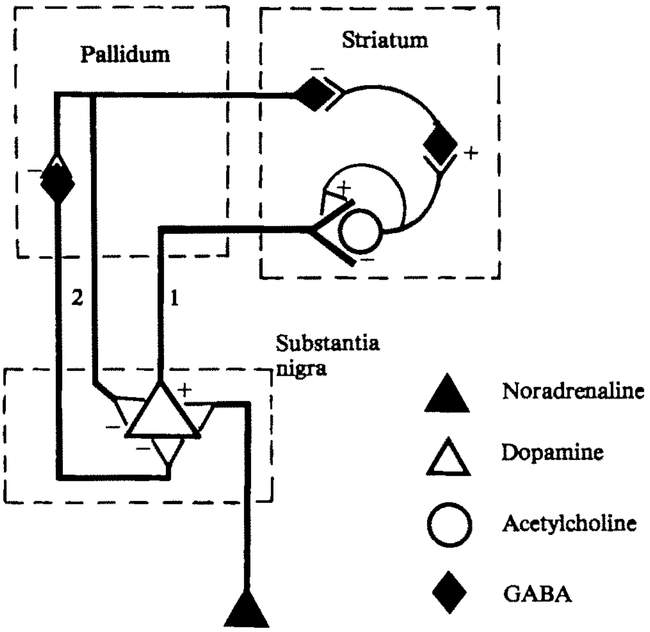

FIG. 4. Proposed neurotransmitter pathways in the basal ganglia. 1, nigrostriatal dopaminergic pathway; 2, striopallidonigral GABA pathways. + = excitatory synapses; − = inhibitory synapses. For references, *see* text.

Measurements of dopamine in post-mortem brain tissue do not seem to be affected by ante-mortem factors such as age, sex, drug administration, long-term stay in hospital, cause of death or agonal status (Spokes, 1979; Bird *et al.*, 1979). Since the post-mortem handling of control, schizophrenic and choreic brain tissue was similar, the present finding of increased dopamine concentrations in the corpus striatum, nucleus accumbens and pars compacta in choreic cases can be regarded as real. Moreover, the increased striatal concentrations of dopamine do not appear to be related to neuroleptic medication as normal dopamine values were observed in striatal tissue from schizophrenic patients, and drug-treated and drug-free choreic subjects had similar dopamine values. Animal studies also support the view that chronic treatment with neuroleptic drugs does not influence striatal dopamine levels (O'Keefe, Sharman and Vogt, 1970; Lloyd, Shibuta, Davidson and Hornykiewicz, 1977).

The present results do not agree with some previous reports. Thus, Bernheimer *et al.* (1973) found normal levels of dopamine in the putamen, pallidum and substantia nigra from choreic subjects, and slightly reduced concentrations in the caudate nucleus, but a maximum of only 10 samples was analysed in any of these brain regions, and in only 4 cases was the diagnosis of Huntington's chorea histologically confirmed. Bird and Iversen (1974), reporting on a larger series of 22 cases, found normal levels of dopamine in the striatum. However, some of their choreic brain specimens had not been deep frozen at autopsy but had, instead, been transported to the laboratory chilled on ice, involving a delay of several hours. A considerable loss of dopamine could have occurred under such conditions (Sloviter and Connor, 1977). In the present study a larger control and choreic series has been used and a standardized system of brain collection employed.

The interpretation of the regional increases in dopamine concentrations in Huntington's chorea can be only speculative. Perhaps the most likely explanation is that they arise from a greater density of dopaminergic terminals in the striatum, which is undergoing shrinkage, in the presence of a largely intact nigrostriatal projection. In end-stage Huntington's chorea there is a marked (about 60 per cent) loss of tissue volume, affecting each of the anatomical divisions of the corpus striatum to a similar degree (Lange, Thörner, Hopf and Schröder, 1976), whereas there is no evidence of prominent cell loss from the pars compacta of the substantia nigra (Bruyn, 1968) and intrastriatal dopaminergic fibres appear to be intact (Sluga, 1966). Atrophy of the corpus striatum of the magnitude described by Lange *et al.* (1976) might be expected to produce a 150 per cent increase in the dopamine concentration of the remaining tissue, if the net content of dopamine were unchanged. The increase, however, was only about 70 per cent in the putamen and pallidum, and only 32 per cent in the caudate nucleus. The total content of dopamine in the choreic corpus striatum is, therefore, likely to be considerably reduced. However, tissue shrinkage *per se* would be expected to produce a uniform increase in dopamine concentration throughout the corpus striatum. That this does not occur indicates that other factors may also be involved, such as a differential retrograde loss of dopaminergic terminals.

Measurements of dopamine concentrations alone provide little indication of the functional activity of dopaminergic systems, but this can be assessed by estimations of brain concentrations of the major dopamine metabolite, homovanillic acid (HVA), formed from the metabolism of dopamine released at synapses (Roffler-Tarlov, Sharman and Tegerdine, 1971). Since about 75 per cent of the dopamine in mammalian brain is present in the nigrostriatal system, the level of HVA measured in lumbar cerebrospinal fluid (CSF) is believed largely to reflect the functional activity of this pathway. There have been several reports of reduced HVA concentrations in CSF (about 50 per cent normal) in Huntington's chorea (Curzon, Gumpert and Sharpe, 1972; Chase, 1973; Caraceni, Calderini, Consolazione, Riva, Algeri, Girotti, Spreafico, Branciforti, Dall'Olio and Morselli, 1977), suggesting that the turnover of the remaining dopamine in the corpus striatum is normal or slightly reduced. However, HVA concentration in CSF may also depend on ventricular volume and the decreased HVA concentrations in CSF from choreic subjects may, to some extent, be related to ventricular dilatation (Curzon, 1975). CSF levels of HVA have been shown to be particularly low in rigid choreic patients (Curzon *et al.*, 1972; Johansson and Roos, 1974; Caraceni *et al.*, 1977). In the present study, striatal dopamine values in rigid choreic subjects tended to be lower than those in non-rigid cases, but the differences were not statistically significant; but rigid cases of Huntington's chorea show especially marked atrophy of the corpus striatum (Liss, Paulson and Sommer, 1973), and hence the net dopamine content in such patients is likely to be very low.

The extrapyramidal dysfunction in Huntington's chorea cannot, therefore, be attributed to an absolute overactivity of the nigrostriatal system, but it remains possible that there is a relative overactivity in the nigrostriatal pathway, arising from either a deficiency in a neurotransmitter system which is normally antagonistic to dopamine, or, as proposed by Klawans (1970), from hypersensitivity of striatal postsynaptic dopamine receptors. Receptor hypersensitivity may be responsible for the choreiform movements which can complicate the administration of L-dopa or dopamine agonists, such as bromocriptine, to parkinsonian patients (Calne, Teychenne, Claveria, Eastman, Greenacre and Petrie, 1974), and could arise from dopaminergic denervation of striatal cells, a hypothesis supported by animal studies (Ungerstedt, Ljungberg, Hoffer and Siggins, 1975). However, in Huntington's chorea the nigrostriatal system does not degenerate to provide a stimulus for the development of supersensitive postsynaptic dopamine receptors. Moreover, measurements of the density of dopamine receptors in striatal tissue at autopsy have shown a significant decrease in Huntington's chorea (Reisine, Fields, Bird, Spokes and Yamamura, 1978). The available evidence suggests, therefore, that relative dopamine overactivity results from the loss of a neurotransmitter system which normally opposes the action of dopamine, either at the same striatal target cells as those innervated by dopaminergic terminals, or by participating in an interneuronal feedback mechanism which inhibits activity in dopaminergic neurons.

Tissue shrinkage may also explain the increased concentration of dopamine in the substantia nigra noted in the present study and previously by Bird (1976). In Huntington's chorea the substantia nigra often appears darker than normal (Bird, 1976) and shows a loss of volume (E. G. S. Spokes, unpublished observations), perhaps indicating a condensation of pigmented dopaminergic cell bodies. Consistent with this interpretation, Bird (1976) reported a twofold increase in tyrosine hydroxylase activity in the choreic substantia nigra, this enzyme being a marker for catecholamine-containing cells, and Enna and his co-workers (Enna, Bennett, Bylund, Snyder, Bird and Iversen, 1976) found an increase of similar magnitude in the density of receptors for GABA believed to be situated on the cell bodies and dendrites of the dopaminergic cells in this brain region.

The increased levels of dopamine observed in the nucleus accumbens in choreic and schizophrenic subjects may be related to the symptom complex of schizophrenia, which is sometimes a prominent feature in Huntington's chorea. Indeed, it has been suggested that these diseases have an anatomical-biochemical relationship (Klawans, Goetz and Westheimer, 1972). Alternatively, this finding may reflect chronic neuroleptic treatment, as long-term administration of neuroleptic drugs can selectively increase dopamine concentrations in limbic areas in experimental animals (Lloyd *et al.*, 1977). However, the increases observed in Huntington's chorea occurred irrespective of neuroleptic administration. Elevated levels of dopamine in the nucleus accumbens might also be a function of tissue shrinkage, as this structure is anatomically part of the striatal complex, but the nucleus accumbens usually shows considerably less atrophy than the remainder of the striatum (Bruyn, 1968). It is surprising, therefore, that the increase in dopamine concentration observed in this region of choreic brain (87 per cent) is out of proportion to the 32 per cent increase present in the head and body of the caudate nucleus, again indicating that factors apart from tissue atrophy may be implicated in producing elevated dopamine concentrations.

In addition to the possibility that dopaminergic imbalance in the nucleus accumbens provides the biochemical substrate for the expression of psychotic features, recent evidence from animal studies suggests that this brain region may also be involved in motor function (*see* Costall and Naylor, 1978), especially in controlling movements of the face and jaws, and it is possible that involuntary facial movements may correspond to the repetitive peri-oral movements observed in animals as a result of enhanced dopaminergic effects in the nucleus accumbens.

Noradrenergic pathways in mammalian brain are well documented (Dahlström and Fuxe, 1964; Ungerstedt, 1971), and arise from cell bodies in the hindbrain, the largest group of which form the locus coeruleus. Biochemical analyses of human post-mortem brain tissue have indicated that the basal ganglia contain very little noradrenaline (Ehringer and Hornykiewicz, 1960; Fahn, Libsch and Cutler, 1971) and the role of the noradrenergic system in extrapyramidal function is unknown. However, noradrenaline depletion in the basal ganglia and other brain regions is a feature of Parkinson's disease (Ehringer and Hornykiewicz, 1960; Farley and Hornykiewicz, 1976) and the Shy-Drager syndrome (Spokes, Bannister and Oppenheimer, 1979), and may be implicated in the clinical picture of parkinsonism. It is likely that at least some administered L-dopa is converted to noradrenaline in the brain, and animal experiments suggest that this process may contribute to this drug's anti-akinesia effect (*see* Pycock, 1978). Dopamine and noradrenaline may therefore exert a synergistic influence on some aspects of basal ganglia activity.

Bernheimer and Hornykiewicz (1973) reported that noradrenaline levels were normal in striatal tissue from choreic subjects, but in the present study, significantly elevated noradrenaline concentrations were demonstrated in the caudate nucleus, lateral pallidum and pars reticulata. No difference was found between noradrenaline values in choreic patients receiving neuroleptics and those not receiving such medication, and striatal noradrenaline concentrations were normal in the schizophrenic cases. These observations suggest that long-term neuroleptic treatment does not influence striatal noradrenaline values, in agreement with findings in experimental animals (Lloyd *et al.*, 1977). Central noradrenergic pathways are not known to be involved in Huntington's chorea and prominent pathological changes have not been reported in the locus coeruleus, suggesting that noradrenergic neurons are probably intact. This proposition is supported by the observation that noradrenaline concentrations are normal in brain regions unaffected by pathology in Huntington's chorea, such as the red nucleus and septal nuclei.

The mechanism underlying the regional increases in noradrenaline concentrations in Huntington's chorea is again open to speculation. Although tissue shrinkage may be a factor it does not explain the selectivity of the changes, and such increases as are present are not in proportion to the degree of tissue atrophy. This finding, together with the presence of normal noradrenaline concentrations in brain regions showing a gross reduction in volume, such as the putamen and medial pallidum, indicates that there is a considerable net loss of noradrenaline from the corpus striatum. This may arise from a loss of noradrenergic terminals in proportion to the degree of tissue atrophy or, perhaps, is a function of adaptive changes in such fibres.

Evidence has already been cited that noradrenaline may act synergistically with dopamine, particularly with respect to the anti-akinesia effect of L-dopa. If this were the case, the persisting availability of noradrenaline, perhaps at the level of the substantia nigra, in the presence of a deficiency of a neurotransmitter system which normally antagonizes the dopamine influence in the striatum, might contribute to the apparent dopaminergic overactivity in chorea (fig. 4).

Studies on the distribution of GABA and GAD in the mammalian brain, including that of man, have shown that the highest levels of each are in the pallidum and substantia nigra, with high levels in the striatum also (Fahn and Côté, 1968; Bird and Iversen, 1974; McGeer and McGeer, 1976; Okada, 1976). Within the striatum, most GAD appears to be localized in small inhibitory interneurons, Golgi type II cells (McGeer and McGeer, 1975) although some may be present in the cell bodies of GABA-containing striatal output neurons whose terminals synapse in the pallidum and substantia nigra (Kim, Bak, Hassler and Okada, 1971; Yoshida and Precht, 1971; Precht and Yoshida, 1971) (fig. 4). Other studies have indicated that a major GABA pathway originates in the pallidum and innervates dopaminergic neurons in the substantia nigra (Hattori, Fibiger and McGeer, 1975) (fig. 4). The striopallidonigral GABA pathways exert an inhibitory influence on target dopaminergic cells, thereby reducing activity in the nigrostriatal tract (*see* Bunney and Aghajanian, 1976).

Reduced GAD activity in the basal ganglia of choreic patients has been reported by several groups of workers (McGeer, McGeer and Fibiger, 1973; Bird and Iversen, 1974; McGeer and McGeer, 1976; Spokes, Garrett and Iversen, 1979), the levels being reduced by about 80 per cent when compared with normal control material. Reductions in the concentration of GABA also occur in these brain regions, although to a lesser degree (Perry *et al.*, 1973; Bird and Iversen, 1974; Urquhart, Perry, Hansen and Kennedy, 1975; Spokes *et al.*, 1979). Since loss of striatal neurons is a prominent pathological feature in Huntington's chorea, these findings are believed to reflect the degeneration of both striatal interneurons and output cells to the substantia nigra.

Low levels of GAD activity, however, have been reported in parkinsonism (McGeer and McGeer, 1976; Laaksonen, Reikkinen, Rinne and Sonninen, 1976), schizophrenia (Bird, Spokes, Barnes, Mackay, Iversen and Shepherd, 1977), dementia (Perry *et al.*, 1977; Bowen *et al.*, 1974, 1976) and depression (Perry *et al.*, 1977). The interpretation of these findings is made difficult by the observation that agonal status has a profound influence on measurements of GAD activity in post-mortem brain (Bowen *et al.*, 1976; McGeer and McGeer, 1976; Perry *et al.*, 1977; Bird *et al.*, 1979; Spokes, 1979). Thus, in many instances, low GAD activities may mirror the influence of factors associated with a protracted terminal illness rather than pathological changes in GABA systems. Indeed, our finding of reduced GAD activity in schizophrenic brain subsequently proved to be explicable solely in terms of such factors (Bird *et al.*, 1979).

The rationale for considering Huntington's chorea as a protracted terminal illness, irrespective of the immediate cause of death, has been explained. Consistent with this argument, the present study shows clearly that the immediate cause of death does not appear to affect the measurement of GAD activity in choreic brain tissue to any great extent. When data from choreic cases were compared with those from control or schizophrenic cases dying from prolonged terminal illnesses, highly significant reductions in GAD activity were found in the striatum and lateral pallidum (about 50 per cent), whereas in other regions the activity was normal. This selective loss of enzyme activity does not appear to be related to chronic hospitalization or neuroleptic medication as normal values were observed in schizophrenic inpatients and values obtained from drug-treated and drug-free choreic cases were similar. In agreement with an earlier report (Bird and Iversen, 1974), no change in GAD activity was observed in association with the development of muscle rigidity in choreic subjects.

GABA appears to be fairly stable in human post-mortem brain (Perry, Buchanan, Kish and Hansen, 1979; Spokes *et al.*, 1979) and, unlike GAD, is largely unaffected by agonal status (Spokes *et al.*, 1979). In a recent study on human post-mortem putamen (Spokes *et al.*, 1979) we have shown that GABA concentrations and GAD activities were reduced by a similar degree (about 50 per cent) in choreic cases, after allowing for ante-mortem factors. This finding is consistent with the view that GABA and GAD in the striatum are present mainly in the interneuron cell population which, in end-stage Huntington's chorea, shows about a 50 per cent loss in numerical density per unit volume of tissue (Lange *et al.*, 1976).

In earlier studies, losses of GAD activity have been reported in the substantia nigra of choreic subjects (Bird and Iversen, 1974; McGeer and McGeer, 1976), but GAD activity in this region is markedly affected by agonal status (Spokes, 1979) and when this ante-mortem factor is allowed for the losses in choreic tissue are no longer apparent. This brings into question the assumption that the proposed

GABA-containing striopallidonigral pathways are involved in the disease, which may also be criticized on the basis of neuropathological observations. Large striatal cells are believed to give origin to striatal efferent fibres (Fox, Andrade, Hillman and Schwyn, 1971/1972; Fox, Andrade, Schwyn and Rafols, 1971/1972) and this cell population remains numerically intact in Huntington's chorea (Lange *et al.*, 1976). However, as previously mentioned, the substantia nigra in this disease does appear to undergo shrinkage and it is possible, therefore, that the loss of fibres is balanced by nigral atrophy and that GABA-containing terminals originate from a population of small striatal cells or pallidal neurons or both. As is the case with the putamen, measurements of GABA levels in the substantia nigra appear to be unaffected by agonal status (Spokes, Garrett and Iversen, 1980) and may provide a more reliable index of the integrity of GABA-containing fibres than measurements of GAD. We have recently shown that GABA is reduced by about 25 per cent in the choreic substantia nigra (Spokes *et al.*, 1980) in agreement with earlier observations (Perry *et al.*, 1973; Urquhart *et al.*, 1975) and consistent with the hypothesis that nigral GABA-containing terminals degenerate in Huntington's chorea. Alternatively, if the findings of normal GAD activity in the choreic substantia nigra (taking into account ante-mortem factors) reflects a normal density of remaining GABA terminals, reduced GABA concentrations might indicate increased release of GABA by these nerve endings. Such an adaptive change, operating through feedback mechanisms, might be expected to limit the apparent overactivity in the dopaminergic nigrostriatal pathway in chorea.

Choline acetyltransferase (CAT) is present in high concentrations in the striatum (Bird and Iversen, 1974; McGeer and McGeer, 1976), and experimental studies have indicated that it is located within cholinergic interneurons which are innervated by dopaminergic terminals (Hattori, Singh, McGeer and McGeer, 1976) (fig. 4).

Dopamine is released tonically in the striatum (Guyenet, Agid, Javoy, Beaujouan, Rossier and Glowinski, 1975) and inhibits acetylcholine release (Bartholini, Stadler, Gadea-Ciria and Lloyd, 1977). In the present study, evidence for cholinergic neuron involvement in Huntington's chorea stems from the finding of reduced CAT activity in the striatum, concurring with the earlier observations of other workers (McGeer *et al.*, 1973; Bird and Iversen, 1974; Aquilonius, Eckernäs and Sundwall, 1975; McGeer and McGeer, 1976). These changes could not be attributed to chronic stay in hospital or neuroleptic treatment, as evinced by the normal values in schizophrenic subjects. Rigid and non-rigid choreic cases had similar striatal CAT values, as noted previously by Bird and Iversen (1974). Clearly, the over-all loss of enzyme activity is more marked when striatal atrophy is taken into account.

A considerable scatter in striatal CAT values was observed in the choreic subjects, in agreement with earlier reports (McGeer *et al.*, 1973; Bird and Iversen, 1974; McGeer and McGeer, 1976). The reason for this finding is not clear, but it has been suggested that CAT loss from the striatum proceeds in a 'patchy' fashion

(McGeer *et al.*, 1973) and Aquilonius *et al.* (1975) produced evidence for such a phenomenon in two choreic cases. In the present study, however, tissue from each anatomical region was finely chopped and mixed so that values obtained for each neurochemical substance in subsequent analyses should be representative of the region as a whole. Moreover, the highly significant correlation between CAT activities in the putamen and caudate nucleus makes it most unlikely that low values arose from the sampling of a low activity tissue 'patch' in either of these areas.

The interpretation of these findings is again conjectural. On anatomical grounds, it may be that levels of CAT activity will depend upon the balance of loss of small cholinergic cells and striatal shrinkage. Alternatively, the changes in CAT activity may reflect an increased inhibitory dopaminergic input, although there was no correlation between dopamine values and CAT activities in the choreic group. The finding of only slightly reduced (17 per cent) CAT activity in the choreic nucleus accumbens is consistent with other reports (McGeer and McGeer, 1976; Aquilonius *et al.*, 1975) and again emphasizes the relative sparing of this area compared with the striatum.

The importance of dopaminergic-cholinergic balance in normal striatal function is well documented and, with the pharmacological evidence for striatal dopamine predominance in chorea, it might be predicted that drugs which facilitate striatal cholinergic neurotransmission should ameliorate choreic movements. The centrally active anticholinergic agent, benztropine, reportedly exacerbates chorea (Klawans and Rubovits, 1972). On the other hand, the results obtained with the centrally active anticholinesterase, physostigmine, have varied, some workers reporting a lessening of choreic movements (Klawans and Rubovits, 1972; Aquilonius and Sjöström, 1971) whereas others failed to obtain consistent effects (Fahn *et al.*, 1971; Tarsy, Leopold and Sax, 1974). Similar discrepencies have been noted with choline administration to choreic patients (Davis, Hollister, Barchas and Berger, 1976; Growdon and Wurtman, 1979), large doses of which elevate acetylcholine concentration in rat brain (Haubrich, Wang, Clody and Wedeking, 1975).

The inconsistent response of choreic patients to facilitated cholinergic function may result from several factors. The depletion in striatal CAT activity may reflect the loss of cholinergic cells so that the capacity for cholinergic 'recovery' may be considerably impaired. Furthermore, the density of striatal muscarinic cholinergic receptors is reduced by some 50 per cent in choreic tissue (Enna *et al.*, 1976; Hiley and Bird, 1974) suggesting a decrease in the cell population which is normally responsive to acetylcholine. Finally, striatal cholinergic neurons exert a positive feedback influence on nigrostriatal dopaminergic cells, increasing dopamine turnover possibly by both a direct action on presynaptic dopamine terminals (Westfall, 1974) and by contributing to a polysynaptic pathway in which their effect is to inhibit activity in the striatonigral GABA system (Bunney and Aghajanian, 1976) (fig. 4). Thus the beneficial effects of increased cholinergic activity may be offset by increased dopamine release and, on balance, it might be anticipated that attempts to facilitate striatal cholinergic function in chorea would meet with little therapeutic success.

In the present study, a 28 per cent reduction in CAT activity was observed in hippocampal tissue from choreic subjects, in contrast to an earlier report of normal values in 8 choreic subjects (McGeer and McGeer, 1976). The hippocampus receives its cholinergic input from the septal region *via* the fornix (Shute and Lewis, 1961) and in the choreic subjects the septal nuclei also showed depleted CAT activity (37 per cent). In both the control and choreic groups there was a highly significant correlation between CAT activities in these two brain regions. Reductions in hippocampal CAT activity have also been reported in senile dementia, particularly of the Alzheimer type (Perry *et al.*, 1977), and it is possible that the cognitive impairment, especially memory dysfunction, associated with these diseases may be related to this finding since central cholinergic systems have been implicated in playing a role in learning processes (Moss and Deutsch, 1975).

SUMMARY

Dopamine, noradrenaline, glutamic acid decarboxylase and choline acetyltransferase were measured in various regions of brain obtained at autopsy from a large series of cases of Huntington's chorea, dying with advanced forms of the disease. Neurochemical values in the choreic cases were compared with those from control and schizophrenic cases.

In brain tissue from choreic patients, highly significant increases in dopamine concentrations were found in the corpus striatum, nucleus accumbens and pars compacta of the substantia nigra. This is consistent with the hypothesis that the nigrostriatal dopamine system is spared and may exert a relatively unopposed action on striatal function.

Noradrenaline concentrations were raised in the caudate nucleus, lateral pallidum and pars reticulata of the substantia nigra, indicating preservation of central noradrenergic pathways.

Glutamic acid decarboxylase activity was reduced in all brain regions examined but, taking ante-mortem factors into account, the depletion was confined to the striatum and lateral pallidum. This is consistent with the view that striatal GABA-containing interneurons degenerate.

Significant losses of choline acetyltransferase activity were observed in the striatum, nucleus accumbens, septal nuclei and hippocampus.

The development of muscle rigidity in choreic patients did not significantly affect the neurochemical values.

The neurochemical alterations in Huntington's chorea could not be attributed to differences in ante-mortem or post-mortem factors between the choreic group and the control and schizophrenic groups.

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NOTICES OF RECENT PUBLICATIONS

The Hippocampus as a Cognitive Map. By JOHN O'KEEFE and LYNN NADEL. 1978. Pp. 570. Oxford University Press. Price £25.00.

The hippocampus remains an enigmatic part of the brain. Representing a structurally simplified area of the cerebral cortex, its function is certainly far from simple to understand. As soon as a closer study is made, clinicians, histologists, physiologists, biochemists and psychologists have all agreed that the apparent simplicity yields to an astonishing complexity. Not least does this paradox apply to the over-all function of the hippocampus—what role does it play in our behaviour? On this point the views have changed greatly over the years, from assigning the hippocampus a role in olfaction through autonomic and emotional control to being the seat for recent memory.

In particular, studies of neurological patients have been important sources for this development. Such studies (Scoville and Milner, 1957; Penfield and Milner, 1958; Milner, Corkin and Teuber, 1968) have led to a nearly general agreement that the hippocampus is centrally involved in memory, if not being the essential structure for this global neural function. However, suggestive as this idea is, there is also a clear dissatisfaction with the theory. There are several reasons for this, not least the difficulty in verifying its basic components in animal experiments (Horel, 1978). In a variety of animals, bilateral hippocampal damage does not lead to the learning and memory deficits predicted from the Scoville-Milner theory.

On this background, the present book presents an alternative explanation of the data on hippocampal damage. As a basis for this re-interpretation, the authors, John O'Keefe and Lynn Nadel, give us a comprehensive and wholly new theory for the functioning of the hippocampus. It is an impressive book. The new theory implies that the hippocampus organizes spatially related information to a cognitive map. The animal then uses this map for its strategy for a wide variety of behaviours. The book is based on a thorough and critical perusal of the large literature in this field. In a commendable way the authors present their theory so that it is clearly understood—and lends itself to experimental tests.

In the first chapter the authors review theories of space and claim that psychological theory has over-emphasized egocentric space at the expense of objective, non-egocentric space. An important conclusion is that there is a clear need for the concept of unitary space, representing a sort of spatial framework. This must be available soon after birth, being necessary for processes of localization, identification and the organization of experience depending upon these processes.

In a chapter on spatial behaviour, the authors discuss different strategies for localization of objects and places. In particular, they emphasize the difference between maps and routes, and stress the superiority of the former. Maps give a greatly increased flexibility in the choice of spatial responses. The brain is assumed to contain a cognitive-mapping system which again contains a map for each environment the organism has experienced. With this map the animal can use the information to solve a wide variety of problems of defence and consummation.

An important distinction in the spatial map theory is that of the taxon and locale systems. The *taxon* system generates routes, relying on sensory inputs as related to egocentric space. In contrast, the *locale* system is a cognitive mapping system which generates place hypotheses and exploration. It is postulated that the locale system is located in the hippocampus whereas the taxon system is extrahippocampal. Therefore, an animal without its hippocampi has to rely on the taxon system for its spatial behaviour.

Much of the inspiration for this interesting theoretical framework comes from the recording from single nerve cells in the hippocampus in freely moving rats in the authors' laboratory and by Dr James B. Ranck at Ann Arbor. The authors distinguish between place and displace units. Place units do not depend upon a particular type of stimulus, but upon the place in which the animal finds itself. The displace units depend upon the behaviour of the animal and not upon its spatial orientation. The latter are closely related to the most prominent feature of the hippocampal electroencephalogram, the theta waves.

An essential element in the spatial map theory is the existence and properties of the place units. The model implies that such cells in the CA1 field (and possibly in the CA3) of the hippocampus receive taxon information through the granule cells of the fascia dentata, which in turn is played upon by cells of the entorhinal area of the hippocampal gyrus. The CA1 neurons are supposed to form place representations by combining the various taxon representations they receive from the dentate fascia. Secondly, the CA1 neurons organize these place representations in a matrix with respect to distance and direction.

It seems to me that the theory has a weak point in that the authors do not give any indication of the morphology of the proposed map. Nor do they hint at how the map is represented in discharge pattern of the participating neurons. These objections, coupled to the often modest increase of the discharge frequency shown by the place cells when the animal is in the correct area makes it uncertain what particular role a cell may play in the spatial behavioural repertoire. Another surprising finding, not well accounted for by the theory, is that neighbouring cells may differ widely in their discharge patterns. With the strict organization of hippocampal neurons in interconnecting chains or lamellæ one would expect a more systematic behaviour of cells lying close together if their main function has been tested. Or—it may be that the sampling of cells is too capricious to reflect a sufficiently detailed map of the cells that participate in a given place-specific representation?

Another point deserving some concern is the link between the postulated hippocampal machinery and the motor systems. With the remarkable short latencies between the onset of theta activity and certain motor responses, the link must be relatively close. One would expect that routine reactions involving the taxon system should have shorter motor latencies than those of the locale system since the latter allows more varied and complicated responses.

The main impression of the book is that O'Keefe and Nadel have provided us with an interesting and well-formulated theory for hippocampal function. The hypothesis not only allows a reinterpretation of the many lesion experiments which the authors have surveyed critically, but it may serve as a basis for new experimental and clinical tests. An important result may be the redefinition of the role the hippocampus plays in memory. May be this structure is only essential for a part of memory, namely, that related to cognitive spatial tasks.

In my opinion the book will be extremely valuable for future studies on hippocampal function, both clinical and experimental. The authors have performed an impressive task, for which many of their fellow scientists are, and will be, grateful indeed.

PER ANDERSEN

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Brain Death: Interrelated Medical and Social Issues. Edited by JULIUS KOREIN. 1978. Pp. 454. Annals of the New York Academy of Sciences, **35**. Price $59.00.

'The times have been that when the brains were out the man would die'. *Macbeth, Act III, Scene 4*

Brain death is an artefact of nature, a product of technical developments in medicine which have made it possible for cardiorespiratory function to continue for days after the brain is irreversibly damaged. It was first described as *coma dépassé* by Mollaret and Goulon in 1959; but it was the papers from Harvard (Ad hoc Committee, 1968; Beecher, 1969) which began the debate about how to recognize this state reliably, and what to do when it had been diagnosed. In most countries that debate is now largely over. There is a consensus that diagnosis is usually possible on clinical grounds alone, and that the proper course is then to declare the patient dead and to discontinue mechanical ventilation. To that extent brain death is no longer a live issue.

However, different countries have reached their present *modus vivendi* with brain death by different routes, which reflect national attitudes to their doctors and to issues pertaining to life and death. In Britain the Department of Health and Social Security set up a small clinical working party in 1974, which produced a practical document, recommending criteria for diagnosis. This was then discussed and modified by the Medical Royal Colleges and their Faculties. Their two-page report, published in the *Lancet* (1976) and in the *British Medical Journal* (1976), indicated that EEG was not considered necessary for diagnosis, but that clinical examination by two doctors was. Subsequently an addendum was published which stated that the brain-dead patient should be regarded as legally dead (*British Medical Journal*, 1979); no change in legislation was considered necessary. The Chief Medical Officer of the Department of Health sent copies of these papers to all hospital doctors, together with a model check-list for the diagnosis of brain death, as recommended guidelines. These few pages seem to contain all that need be said about brain death, British style.

In America it is different. The 450 closely written pages of this book, recording a conference held in New York in 1977, deal not only with brain death but with the problems and ethical issues associated with prolonged non-cognitive survival, and with the pressures for withdrawing treatment from the terminally ill who are not (yet) brain-dead. The canvas is a broad one, with history, theology, philosophy, biochemistry, electrophysiology, radiology, pathology—and lots of law. This is brain death, American style.

The development of attitudes about brain death and the vegetative state are described. Some have sought to emphasize that there are two kinds of death—brain death and cardiorespiratory arrest; others emphasize that cardiorespiratory arrest is normally followed very rapidly by brain death, unless there is some artificial intervention. It can therefore be argued that traditional death (cardiorespiratory arrest) is synonymous with brain death—which is therefore not as novel a concept as is sometimes thought. These two views are reflected in the drafting of different American statutes about brain death in various States; some of these follow the unitary doctrine of death, whilst others emphasize the distinction between death of the brain and cardiorespiratory arrest. The hope is expressed that a uniform act (for all States) may emerge, as it did for transplantation of organs and tissues.

There follow excellent accounts of clinical criteria, including a painstaking analysis of the disappearance of various clinical reflexes at different time periods after apnœa or EEG silence. The changes in blood gases during disconnection from the ventilator are described in detail in another chapter, which provides adequate evidence that under proper conditions a period of fifteen to twenty minutes apnœa does not threaten the patient's oxygenation or hæmodynamic state; no added stimulus to respiration results from allowing the $P_{a}CO_2$ to rise above 60 mm Hg, but higher levels may be harmful. The facts and figures contained in these two chapters provide the kind of solid reassurance needed to convince anæsthetists and physicians in intensive care units who are still doubters, but who are anxious not to prolong the charade of ventilating a corpse. They know that to do so deprives death of dignity, distresses relatives, and is wasteful of scarce resources—yet they remain unsure of what action is appropriate.

Three chapters on the EEG are refreshing in their modesty, and in the frankness with which the limitations and pitfalls are described. Several authors (and additional footnotes from the Editor) emphasize that electrocerebral silence is not synonymous with brain death and that the EEG should never be the sole criterion of diagnosis. In spite of this, and the fact that some codes of practice do not require EEG, it is acknowledged that the use of EEG to confirm brain death is still practically universal. However, there is obvious ambivalence on this issue. The British Royal Colleges are scolded for 'de-emphasising and down-playing' the EEG; the argument that this is not universally available is dismissed with the comment that the diagnosis of brain death is likely to be undertaken only in hospitals where EEGs are available. Whatever the situation in other countries, there are EEG machines in only about 10 per cent of acute general hospitals in Britain, any of which are now likely to encounter cases of brain death. One American speaker said that he told his technicians that brain death records were the most important that they ever ran, whilst another said that brain death records should be read only by a Board-certified staff member. However, another American questioned the wisdom of interrupting the useful investigation of the living by the unnecessary investigation of the dead.

A number of fragmentary chapters follow, describing the wide range of other laboratory tests which have been used to confirm brain death, including measures of the cerebral circulation by radiology, isotopes, echo and CT scanning. These various methods have been of passing interest in explaining the phenomenology of brain death; but they are not realistic measures for routine diagnostic use. Indeed the discussion at the end of this section includes the practical plea that the diagnosis of brain death should not depend on tests that are inaccessible to the non-neurologist, nor should it need a neurophysiologist.

There is an admirable paper by Posner on the clinical differentiation of brain death from coma and other states of reduced consciousness. The features, evaluation and outcome of patients who become vegetative after non-traumatic coma are well described in another chapter, on the basis of an Anglo-American collaborative study. The legal aspects of the 'right to die' movements in the US indicate how medicine and society elsewhere deal with the problem of the termination of care for the terminally ill. It is acknowledged that this is an area of much wider significance than brain death, and one about which solutions will not come easily. What is extraordinary or excessive treatment, what is undue distress, what is loss of dignity? The need is to try for consensus, and in this area in particular legislation seems inappropriate. There is already some evidence of a consensus that survival in the vegetative state is worse than death (Jennett, 1976).

This book has an abundance of references and the Editor adds helpful short footnotes from time to time where there is confusion on terminology between different authors, or to add an explanation, even a more recent reference. There is an adequate index both to subjects and to authors, including their contributions to discussion. However, there is no list of authors which indicates in detail their discipline or post, although their institution is given at each chapter head. It is curious how frustrating it is not to know more about the credentials of those who express views about issues as volatile and emotional as these; even the denominational affiliation of the theologians has to be surmised from circumstantial evidence.

This book is invaluable as a source of reference, and as a historical document of late-seventies thinking about these issues and conditions. For all that is said, however, the only condition really likely to be confused with brain death is coma due to drugs; all the sensational stories of supposedly unexpected recovery after suspicion of brain death prove to be due to drugs. This has never been better described than in the early British literature (Shakespeare, 1597).

'And this distilled liquor drink thou off,
When presently through all thy veins shall run
A cold and drowsy humour; for no pulse
Shall keep his native progress, but surcease:
No warmth, no breath, shall testify thou livest;

> The roses in thy lips and cheeks shall fade
> To paly ashes; thy eye's window fall,
> Like death, when he shuts up the day of life;
> Each part, deprived of supple government,
> Shall stiff, and stark and cold, appear like death:
> And in this borrowed likeness of shrunk death
> Thou shalt continue two and forty hours
> And then awake, as from a pleasant sleep'.

BRYAN JENNETT

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Endorphins in Mental Health Research. Edited by E. USDIN, W. E. BUNNEY and N. S. KLINE. 1979. Pp. 618. London: Macmillan. Price £22.50.

This book is a report on a symposium which took place in December 1977 in Puerto Rico. It was published in 1979, and there is inevitable overlap with the Proceedings of the International Narcotic Research Conference which met in Holland in July 1978 and appeared in the same year. However, only 18 scientists participated in both meetings. While the accent of the Puerto Rico Conference is on the role of endorphins in mental health, this more specialized aspect fills only a relatively small part of the book and is preceded by three large sections headed 'basic studies'. They deal with localization, chemical structure, biosynthesis and degradation of endorphins, as well as with what little is known of their action in animal and man. They create for the reader to whom the subject is new, the background necessary for the appreciation of the clinical chapters.

One of the most important tools used to reveal the possible contribution of endogenous opioids to normal and abnormal behaviour is naloxone, a highly specific opioid antagonist which has the further advantage of a short half-life in the organism. The effect of naloxone on healthy subjects was therefore studied by a large group of workers from the National Institute of Mental Health. The study led to the unexpected result that pain insensitive individuals showed hyperalgesia after naloxone, whereas pain-sensitive people responded with some degree of analgesia. The authors also observed a reduced response to pain in a subgroup of depressives, but failed to obtain evidence for a beneficial effect of naloxone in any mental disease. Another group tried naloxone on hallucinating patients without success, in spite of previous claims and the observation that naloxone antagonizes certain abnormal activities elicited by LSD in the cat. In contrast, a group of workers in Stanford University appeared to have some success in suppressing hallucinations with naloxone. Psychiatrists from Munich tested both a low and a high dose of naloxone and reported some suppression of hallucinations; the effect was not dose-dependent. A large dose of naloxone was tested on manic patients and, perhaps not surprisingly, was found to have a calming effect.

That the physiological role of endorphins is a complex one is suggested by the variable effects of naloxone in normal volunteers. Some may experience depression, fatigue or decreased vigour, while others remain unaffected. The variability is likely to reflect differences in endorphin production in the subjects.

There are four reports on the administration of β-endorphin to patients suffering either from depression or pain; short-lived improvements were observed, as well as temporary absence of narcotic abstinence symptoms.

The last six chapters deal with the concentration of opioids found in body tissues, including that of some substances which are not peptides.

This book is useful both as an introduction to the opioid field and as a summary of the clinical information available at the end of 1977. The many gaps in our knowledge should stimulate further work on the obviously important role played by the endogenous opioids.

M. VOGT

Recent Advances in Neuropathology. No. 1. Edited by W. T. SMITH and J. B. CAVANAGH. 1979. Pp. 325. Edinburgh: Churchill Livingstone. Price £19.00.

This multiple-author book consists of twelve chapters on various topics written by eminent workers in clinical neuropathology and neurobiology. Most of the contributions are liberally illustrated and contain a comprehensive bibliography.

The first chapter is an excellent review of recent developments in the field of tracer techniques and covers the use of enzyme markers and fluorochrome, and radiolabelled and electron-opaque tracers. The application of these techniques to the study of the blood-brain and blood-nerve barriers in health and disease are described. Orthograde and retrograde axoplasmic flow are also reviewed. In the second chapter the principal features of vasogenic and cytotoxic cerebral œdema are outlined. This is achieved by describing normal and disordered blood-brain barrier, and the vulnerability of various cellular and subcellular components of the nervous system to toxic agents. Some of the complexities of cerebral ischæmia are also covered, though rather superficially, and there is inadequate mention of the current techniques used to determine cerebral blood flow and metabolism. Cerebral œdema and ischæmia are brought together in an analysis of ischæmic cerebral œdema, which is considered to be complex in nature, involving both vasogenic and cytotoxic mechanisms.

The application of cell turnover studies to neuropathology is comprehensively covered in the third chapter in which a description of the cell cycle precedes studies on the developing and mature brain, cell death and the influence of nutrition, hormones and drugs on cell turnover in the nervous system. Data is also given on the study of CNS tumours and both normal and diseased muscle and peripheral nerve. Regeneration in the central nervous system is well reviewed in the fourth chapter. The development of scar tissue is detailed and the generally accepted theory of the failure of central axons to regenerate (the 'barrier hypothesis') is described. Examples of successful regeneration are cited and the influence of various drugs, hormones, growth factors and neurotransmitter substances is described. The demonstration of collateral sprouting in uninjured fibres indicates the potential for axonal growth in the adult CNS and the failure of most injured fibres to grow suggests that it is axonal injury that is the prime inhibiting factor. It is concluded that there is no good evidence for the hypothesis that scar tissue *per se* acts as an impenetrable barrier to growing axons.

The principles and possible scope of image-analysing systems are described in the fifth chapter in which there is a useful account of the equipment and the requirements of good tissue preparation. Reference is made to studies of the CNS using this technique and the expectation is expressed that advances in technology will allow general purpose parallel systems in which all parts of the image are examined and processed simultaneously. Changes that are commonly found in the aged human brain are described in the sixth chapter. These are covered under the main headings of gross changes, such as weight and volume, and the microscopic features of old age that include amongst others loss of nerve cells, accumulation of lipofuscin, changes in cortical dendrites, Alzheimer's neurofibrillary degeneration, senile plaques, granulovacuolar degeneration and the deposition of amyloid. The advantages and disadvantages of using post-mortem material are discussed, though it is admitted that in many respects the most limiting factors at present are technical. It is concluded that the future development of automated and computerized instruments capable of measuring and counting various features in biological material is the key to major advances in the study of the ageing brain.

The seventh and eighth chapters are concerned with tumours of the nervous system. The induction of tumours by the systemic administration of chemical carcinogens is described in chapter seven. The metabolism of various neuro-oncogenic agents is detailed and a lucid account of the biological consequences of DNA alkylation and its repair, the correlation with organ-specific tumour induction and the relationship between chemical carcinogens in the nervous system and the somatic mutation theory of cancer are given. In chapter eight recent developments in the pathology of tumours of the human nervous system, either following the application of new techniques to common tumours or as new information on rarities, are surveyed. Under the heading of neuroepithelial tumours a useful account is given of the correlation between the normal stages of neurocytogenesis and embryonal tumours. Variants of meningiomas and tumours of nerve sheaths are detailed. The current difficulties in classifying primary lymphoid tumours of the nervous system and their increased incidence in primary immunodeficiency disorders and after organ transplantation are discussed. The last part of this chapter includes an update of tumours arising in the pineal gland.

The pathogenesis of spina bifida and related malformations is reviewed in chapter nine. It is commonly believed that variants of spina bifida in which the cord appears open are due to failure of the neural tube to close, but there is also evidence for the alternative hypothesis that a previously closed neural tube can re-open. It is argued that forking of the neural tube may be important in the formation of diastematomyelia. Genetic and environmental factors are discussed and the prenatal diagnosis of these conditions is reviewed briefly. Recent advances in the understanding of the mode of action of mercury, lead and thallium are described in chapter ten. It is concluded that the lesions caused by methyl mercury and inorganic mercury in the nerve cell seem to be essentially the same, though differences in the rate at which the various forms of mercury enter the brain and the time they remain there play an important part in determining the character of the clinical disease they induce. The target organelle in mercury poisoning appears to be the ribosome. Clinical and experimental work suggest that the peripheral neuropathy of lead intoxication is possibly due to a combination of partial demyelination and entrapment. The pathogenesis of lead encephalopathy, on the other hand, remains unclear but there is increasing awareness and concern about the possible long-term (late effects) of lead intoxication, especially in children. Thallium poisoning is known amongst other things to induce peripheral neuropathy and alopecia. The precise site of action is not known but recent evidence suggests that thallium neuropathy may be due to a block in the energy production mechanism of the nerve fibre.

The pathological features of multiple sclerosis are described and analysed with respect to their significance in a better understanding of the disease process in chapter eleven: the possible role of the occlusion of small veins in the brain by aggregates of platelets is also discussed. Amongst the main theories of the ætiology immunological mechanisms and possible viral agents of multiple sclerosis are outlined whereas the role of unsaturated fatty acids gets a particular mention. The hypothesis that multiple sclerosis develops upon a background of an inborn error in the handling of unsaturated fatty acids (the Thompson anomaly) is elaborated and its significance in both the prevention of the anomaly and its recognition by *in vitro* techniques are discussed at some length. Chapter twelve gives an interesting account of the neuropathology of Parkinsonism. The contribution made by histopathology is shown by the identification of a number of subtypes. A better understanding of these variants has come from methods used to map out the anatomical distribution of monoamine, cholinergic and gamma-butyric acid nerve systems. Advances in the histochemistry of Parkinson's disease have indicated that it is a 'structural dopamine deficiency syndrome', though recent work has shown the position to be more complex than perhaps appreciated initially.

All the chapters have been written by experts and therefore it is difficult to give a critical review of what is essentially a book comprised of a series of monographs on diverse topics. However, the text makes interesting reading and is sufficiently well written and informative to give considerable insight into the 'way ahead'. The series 'Recent Advances' in various subjects is now well established and the introduction of one in neuropathology is greatly welcomed. Volume 1 is a good beginning and should lay the foundation for future volumes. There is sufficient information on a wide variety of subjects for it to be possible to recommend this volume strongly to anyone with an interest in the neurosciences, whether clinical or laboratory based.

D. I. GRAHAM

A Textbook of Neurology. H. HOUSTON MERRITT. 5th Edition. 1979. Pp. 961. London: Henry Kimpton. Price £18·20.

Dr Houston Merritt worked on this latest edition of his book until shortly before his recent death. He wrote practically the whole of the first edition, published in 1955, but he was joined by ten other American neurologists for the sixth. Merritt's book represents a complete contrast with Russell Brain's, the two works are so dissimilar that they can be regarded as complementary rather than competing. Each book represents the man.

Dr Merritt regarded accounts of the anatomy and physiology of the nervous system as unnecessary for his textbook. Students and trainee neurologists have an ample choice of texts available in these fields. He eschewed chapters on the neurological examination for the same reason. Lastly, he refused to incorporate an account of speech disorder because he thought the topic unimportant in a practical sense. In response to a mild objection from this reviewer he replied 'There will be no chapter on dysphasia in any book I write'. The succinct style of *A Textbook of Neurology* reflects Merritt's complete lack of verbosity or pomposity. His terse writing sometimes concealed the amount of information he distilled.

Historical and epidemiological aspects of the various neurological disorders considered set the scene for clinical and pathological description throughout the book. The volume is intended for medical students and young men training in general medicine as well as medical and surgical neurology. Nevertheless, many neurologists use Merritt; Sir Charles Symonds was wont to commend it to colleagues and juniors, and I am glad to do the same.

R. A. HENSON

Current Neurology. Volume 2. Edited by H. RICHARD TYLER and DAVID M. DAWSON. 1979. Pp. 531. Boston: Houghton Mifflin. Price $42.50.

This is the second volume of a series designed to acquaint the clinical neurologist with advancing knowledge in his subject. Eleven of the 26 chapters present summaries of progress in subjects covered in the first volume, apparently published last year, while 15 are devoted to new topics. Doctors Tyler and Dawson had a good idea which they have pursued successfully to fruition. There are sections on disorders of muscle, nerve and the central nervous system. Further chapters deal with higher cortical function, basic neuroscience, diagnostic studies and the neurological aspects of medical disease. Clearly, this book performs a useful function in acquainting clinicians with the latest neurological news, though some of this will naturally prove to be ephemeral. The type is excellent, the references are recent and culled from many sources. *Current Neurology* is an excellent book for neurologists in training and established clinicians working in relative isolation. Neurologists with special interests are unlikely to find many unsuspected treasures in their particular fields but they can profit from the whole exercise.

R. A. HENSON

1979 Year Book of Neurology and Neurosurgery. Edited by RUSSELL N. DE JONG and OSCAR SUGAR. 1979. Pp. 472. Chicago and London: Year Book Medical Publishers. Price £20·50.

The familiar pattern of the *Year Book* is preserved in the current edition which is largely devoted to reviews of papers published in 1977. The journals surveyed are predominantly ones which medical and surgical neurologists read of necessity; nevertheless there is a practical value in the publication, not least in the editorial comments appended by Doctors De Jong and Sugar. The *Year Book* is a useful annual addition to departmental libraries, for it constitutes a reliable source for revision; the need for this can be rapidly established by reading and answering the questions set on pages 7 to 10.

R. A. HENSON

FORTHCOMING EVENTS

The Tenth International Congress of Electroencephalography and Clinical Neurophysiology will be held in Kyoto, Japan from September 13 to 18, 1981. This meeting will be followed immediately by the Epilepsy International Congress and the Twelfth World Congress of Neurology, both in Kyoto.

For further information on the Electroencephalography and Clinical Neurophysiology meeting, write to:

Dr Mitsuru Ebe
Secretary, 10th ICECN
Crescent Plaza 103,
4-6 Minami-Aoyama 2-Chome
Minato-ku, Tokyo 107, Japan.

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The Guarantors of BRAIN are prepared to contribute to the cost of travel of neuroscientists under the age of 40 years attending meetings to present their own work or visiting centres of importance to their research. Applicants should be working in the United Kingdom and should provide details of the post held, the nature of the research, the projected visit and estimated cost. When appropriate, applications should be endorsed by the Head of the Department. This offer will be for a trial period limited by the resources available.

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New

DELIRIUM: Acute Brain Failure in Man *by* **Z. J. Lipowski,** *Dartmouth Medical School, Hanover, New Hampshire.* This monograph meticulously details all aspects of the common yet little understood condition of delirium. Initial chapters examine history, etiology, pathophysiology, definition, clinical features, and diagnosis. Subsequent chapters discuss organic causes, differential diagnosis, management, and delirium due to such conditions as drug and alcohol withdrawal, head injury, and brain tumor. Special sections are devoted to delirium encountered in surgery, obstetrics, and geriatrics. *'80, 576 pp., 5 tables, $39.75*

New

MULTIPLE SCLEROSIS IN CHILDHOOD *by* **E. J. Field,** *Royal Victoria Infirmary, Newcastle Upon Tyne, England.* Following an extensive review of the literature, the author demonstrates how a biochemical anomaly affecting unsaturated long chain fatty acids is involved in MS and is reflected in the surface membrane constitution of all body cells, including the oligodendrocyte. He shows how the familial pattern of MS can be identified at an early age and how it is possible, in the adult, to rectify the effects of the inherited anomaly and alter the constitution of myelin so that it is no longer susceptible to the MS process. The text also explains how this information can be used to develop measures for preventing MS. *'80, 120 pp., 18 il. (3 in color), 17 tables, $12.75*

INTRODUCING NEUROPSYCHOLOGY: The Study of Brain and Mind *by* **Stuart J. Dimond,** *Univ. College, Cardiff, Wales.* The initial portion of this text outlines the status of neuropsychology among the brain sciences, the methods used in this discipline, and fundamental brain systems. Remaining chapters focus on the cerebral cortex, the infant brain, the normal brain, mechanisms and functions of the higher mental states, neurological processes in psychiatric illness, and the development of technology for control of the brain. Students and practitioners of neurology will find this book both enlightening and provocative. *'78, 236 pp., 12 il., 2 tables, $15.25*

New

SENSORY INTEGRATION IN CHILDREN: Evoked Potentials and Intersensory Functions in Pediatrics and Psychology *by* **Thorne Shipley,** *Univ. of Miami School of Medicine, Miami, Florida.* Following introductory discussions of evoked cortical potentials (ECP), the author introduces special ECP tests, explains methods for differentiating organic or systemic deficits from psychiatrically or educationally based learning disabilities, and discusses developmental tests of cognitive function. *'80, 176 pp., 56 il., 4 tables, $15.50*

MAJOR NEUROLOGICAL SYNDROMES *by* **Mircea A. Morariu,** *Henry Ford Hospital, Detroit, Michigan.* The author provides comprehensive information on clinical aspects of the most frequently encountered syndromes in neurological practice. Symptoms, signs, and positive diagnostic tests are stressed. Each syndrome is analyzed with regard to history, pathology, pathogenesis, differential diagnosis, and treatment. The diagnostic methodology includes such new noninvasive tests as computerized axial tomography scans. The author also provides an appropriate sequence of studies for each syndrome. A total of thirty-four major neurological syndromes are reviewed, some of which are *Guillain-Barre, Melkersson-Rosenthal* and *Horner's* syndromes. Others include *Amaurosis Fugax, Transient Global Amnesia* and *Akinetic Mutism. '79, 368 pp., 32 il., 6 tables, $24.50*

PREOPERATIVE AND POSTOPERATIVE CARE IN NEUROLOGICAL SURGERY (2nd Ed.) *by* **Burton L. Wise,** *Mount Zion Hospital and Medical Center, San Francisco, California. (3 Contributors)* The first of two sections in this text discusses, among other topics, the cardiovascular and pulmonary systems, pain, wound healing, cerebrospinal fluid leakage, and endocrine management of pituitary-hypothalamic disease. The second segment covers such subjects as normal metabolic responses and requirements, responses to head injury and pneumoencephalography, and vasopressin and acid-base disorders. *'78, 208 pp., 4 il., $15.25*

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Volume 103 Part II June 1980

The Basic Uniformity in Structure of the Neocortex. A. J. Rockel, R. W. Hiorns and T. P. S. Powell 221

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The Clinical Features of Hereditary Motor and Sensory Neuropathy Types I and II. A. E. Harding and P. K. Thomas 259

Course and Prognosis of Multiple Sclerosis Assessed by the Computerized Data Processing of 349 Patients. C. Confavreux, G. Aimard and M. Devic 281

A Physiological Mechanism of Bradykinesia. Mark Hallett and Shahram Khoshbin 301

A Distinct Form of Adult Polyglucosan Body Disease with Massive Involvement of Central and Peripheral Neuronal Processes and Astrocytes: a Report of Four Cases and a Review of the Occurrence of Polyglucosan Bodies in Other Conditions such as Lafora's Disease and Normal Ageing. Yvon Robitaille, Stirling Carpenter, George Karpati and Salvatore DiMauro 315

The Anatomical Basis of Conduction Aphasia. Hanna Damasio and Antonio R. Damasio 337

Effects of Ageing on Local Rates of Cerebral Glucose Utilization in the Rat. C. B. Smith, C. Goochee, S. I. Rapoport and L. Sokoloff 351

Music and Language: Musical Alexia and Agraphia. John C. M. Brust .. 367

Anticipatory Postural Reflexes in Parkinson's Disease and Other Akinetic-rigid Syndromes and in Cerebellar Ataxia. M. M. Traub, J. C. Rothwell and C. D. Marsden 393

The Incidence and Nature of Visual Pathway Involvement in Friedreich's Ataxia. W. M. Carroll, A. Kriss, M. Baraitser, G. Barrett and A. M. Halliday 413

Notices of Recent Publications 435

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The Anatomical Basis of Conduction Aphasia. Hanna Damasio and Antonio R. Damasio 337

Effects of Ageing on Local Rates of Cerebral Glucose Utilization in the Rat. C. B. Smith, C. Goochee, S. I. Rapoport and L. Sokoloff 351

Music and Language: Musical Alexia and Agraphia. John C. M. Brust .. 367

Anticipatory Postural Reflexes in Parkinson's Disease and Other Akinetic-rigid Syndromes and in Cerebellar Ataxia. M. M. Traub, J. C. Rothwell and C. D. Marsden 393

The Incidence and Nature of Visual Pathway Involvement in Friedreich's Ataxia. W. M. Carroll, A. Kriss, M. Baraitser, G. Barrett and A. M. Halliday 413

Notices of Recent Publications 435

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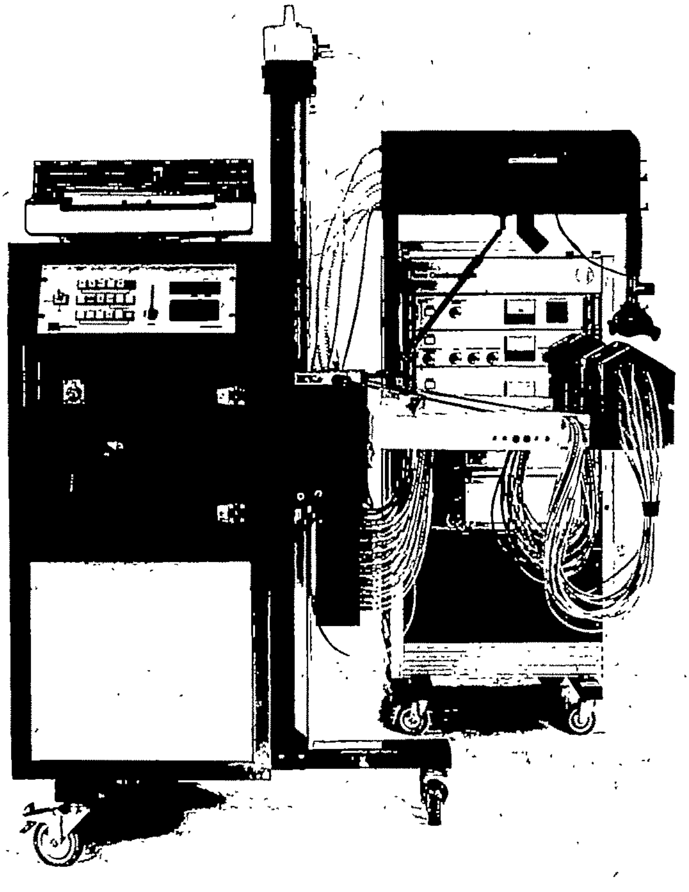

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THE BASIC UNIFORMITY IN STRUCTURE OF THE NEOCORTEX

by A. J. ROCKEL, R. W. HIORNS *and* T. P. S. POWELL

(*From the Departments of Human Anatomy and Biomathematics, University of Oxford*)

INTRODUCTION

SEVERAL quantitative studies have shown that the cell density may vary in different laminæ and in different areas of the neocortex in the same brain and between different species (*see* Tower, 1954; Brody, 1955; Cragg, 1967). The cells are usually most closely packed in layer IV, the density is high in the visual cortex and low in the motor and in general the neurons are more widely separated in larger brains. In an electron microscopic study of the motor cortex of area 4 and of area 3b of the somatic sensory area of the monkey (Sloper, 1973; Sloper, Hiorns and Powell, 1979) the number of neuronal cell bodies was counted in a narrow width through the full depth of the cortex from the pia to the white matter. Surprisingly it was found that despite the marked difference in the thickness of the cortex of these two areas, and their different cytoarchitecture and function, the absolute number of neurons through the cortex was the same and the proportions of the two main cell types, the pyramidal and stellate, were similar. A comparison has now been made of the number of cells through the entire thickness of the cortex in most of the major structural and functional areas in the monkey and in several other species, ranging from mouse to man. With the exception of area 17 of the visual cortex of primates the figures are similar for the different areas, and despite the marked differences in the size of the brains the absolute number of cells through the thickness of the cortex has been found to be constant in the brains of different animals. The results may be of relevance to our understanding of the evolution of this part of the brain, and perhaps to the question of the anatomical basis of the functional columnar organization which is a feature of many areas of the cortex (Mountcastle, 1957, 1978; Hubel and Wiesel, 1962, 1977). A preliminary communication of the results has already appeared (Rockel, Hiorns and Powell, 1974).

MATERIAL AND METHODS

All of the animals (Table 1) were normal adults and the brains were fixed by perfusion through the heart with 0.9 per cent saline followed by 10 per cent formalin. The two human brains were from 26-year-old males who had been killed suddenly in accidents not involving the brain; these were fixed by immersion in 10 per cent formalin after dividing the right and left cerebral hemispheres within a few hours of death. From the human and macaque monkey brains blocks were cut approximately 10 × 5 mm and sufficiently deep to include the entire cortex to be studied together with some of the underlying white matter; the blocks were cut as perpendicular to the surface as possible. The motor and somatic sensory areas were included in one block across the pre- and post-central gyri and which reached to the depth of the central sulcus. The visual cortex of the macaque monkey was studied in blocks which included areas 17 and 18 on the exposed medial and lateral surfaces of the hemispheres, together with part of area 17 lying in the wall of the buried calcarine sulcus; in addition samples were taken throughout area 17 in a 1:10 series of sections of brains in which the entire occipital lobe had been cut in the coronal plane. The visual cortex of the human brains was taken from the posterior and middle thirds of the calcarine sulcus of both hemispheres. The frontal cortex was probably area 9 according to the map of Brodmann, the parietal that of area 7 and the temporal from area 22 in the superior temporal gyrus. Fig. 1 shows the sites in one macaque brain which was typical of all three.

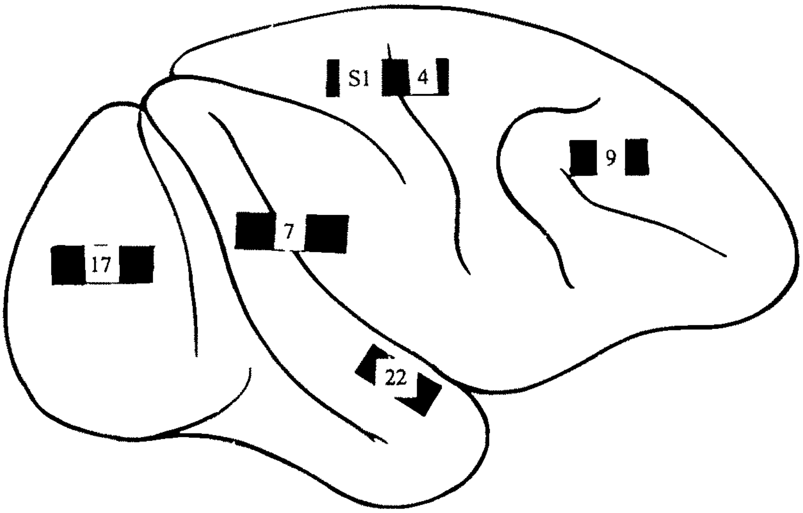


FIG. 1. The sites from which blocks of the neocortex were taken in the macaque monkey.

The cytoarchitectonic features seen in the sections were in accord with the classic descriptions of the respective areas. In the case of the mouse, rat, cat and Tupaia, the entire forebrain was processed as one block. After fixation in formalin the blocks were immersed in 70 per cent alcohol and 2 per cent acetic acid for a few days before being dehydrated and embedded in paraffin wax. Serial sections were cut at 25 μm. The monkey and human blocks were cut perpendicular to the surface of the cortex, with the larger rectangular surface as the cutting edge and the entire forebrain of the smaller animals cut in either the coronal or sagittal planes. A 1:10 series of sections was mounted and stained with thionine. All stages of the histological processing were kept as constant as possible apart from slight differences according to the size of the blocks.

Cell counts of these areas were made using a 10 × eye piece and 100 × oil immersion objective with a ruled graticule in the eyepiece. All neuronal cell somata with distinct nuclei and nucleoli through the thickness of the sections were counted in a width of 30 μm (3 graticule squares) between the pial surface and the white matter. The counts were begun either at the surface or at the level of the white matter and were made in traverses through the cortex as perpendicular to the surface as possible; to do this with a curved surface, an attachment on the moving stage was used by which sections could be rotated independent of the X and Y axes of the moving stage. Thus the absolute number of cells has been counted in a volume of tissue 30 μm (width) by 25 μm (section thickness) through the depth of the cortex.

The cortex of the three macaque monkeys was first sampled and the number of cells in 20 traverses through sections of each area were counted independently by two observers, 40 samples of each area. As there were no significant differences between the mean counts and standard deviations of the two observers the brains of other species were sampled independently, each observer making 10 traverses through each area of one brain of each species.

When it was found that the absolute number of cells in area 17 of the macaque monkey was significantly higher than that in other areas, counts were made in most parts of area 17 of several macaque monkey brains, and blocks of this area were taken from other primates (Table 1) and processed in the same manner. The cortex of the peristriate region, areas 18 and 19, was also sampled in most species.

Although a correction for shrinkage was not required for the interpretation of the results in this study, it was thought of interest to estimate this in the human brain in case the data are used for other studies. One young adult brain, not used for the counts, was obtained unfixed and needles were inserted in the cortex at precisely known distances apart. The brain was bisected and the hemispheres immersed in 10 per cent formalin for several days, and blocks of a similar size and site as those for the counts were taken. The blocks were measured, processed *and cut* (*cf.* Olszewski, 1952, page 12; Phillips, Powell and Shepherd, 1963) in the same way as those for the counts. From measurements of the sections it was found that a linear shrinkage of 18 per cent had occurred due to the fixation and histological processing.

TABLE 1. BRAINS USED FOR SAMPLES OF SIX DIFFERENT CYTOARCHITECTURAL AND FUNCTIONAL AREAS

Species	*No. of brains*	*Areas studied*
Mouse	2	Frontal, motor, somatic sensory, parietal, area 17, temporal
Rat	2	„
Cat	2	„
Monkey	3	„
Man	2	„

Brains used for quantitative studies of area 17 only: Tupaia 1; Galago 1; Marmoset 1; Squirrel monkey 2; Baboon 1; Chimpanzee 1.

RESULTS

The counts in the different areas of the cortex of the macaque monkey confirmed the initial observations (Sloper, 1973; Sloper *et al.*, 1979) that the absolute number of cells in the same narrow width through the entire thickness of area 4 and of area 3b of the somatic sensory area were the same, and they also showed that the same number of cells was present in the association cortex of the frontal, parietal and temporal areas (Table 2). Within the first somatic sensory area in the post-central gyrus the absolute number of cells through the thickness of the cortex was the same in three of its cytoarchitectural subdivisions, areas 3b, 1 and 2. In the striate cortex of area 17 containing the representation of the central 10 degrees of the visual field, however, the number was approximately 2.5 times greater, and it was quite clear at the time of counting that this was due to a much greater density of cells through most of the depth of the cortex but especially in layers II, III and IV. In order to investigate the differences between the observers in counts of the five areas (excluding the visual area) taken from three monkeys a three factor analysis of variance was performed. Observers and areas were taken as 'fixed effects' factors and monkeys taken as a 'random effects' factor. The results of this analysis indicate no difference between the observers (F = 0.47; d.f. = 1,2) or between the areas (F = 0.36; d.f. = 2,4). A difference between monkeys is suggested at the 1 per cent significance level (F = 5.97; d.f. = 2,570). A further analysis of the visual area for monkeys (excluded from the above) indicates no difference between the monkeys counted by two observers (F = 0.33; d.f. = 1,76) but a slight difference at the 5 per cent significance level between the observers (F = 224.97; d.f. = 1,1).

TABLE 2. *MACACA MULATTA.* MEAN AND SD OF 40 COUNTS IN EACH CORTICAL AREA

Motor	110.2 ± 9.4
Somato-sensory	109.4 ± 9.4
Frontal	112.0 ± 11.1
Temporal	109.8 ± 10.3
Parietal	114.6 ± 9.9
Striate	267.9 ± 13.7

Further counts of different parts of area 17, including that in the buried walls of the calcarine sulcus, gave the same figures as in the cortex on the lateral surface of the hemisphere. Although it was thought to be important to count the number of cells in the region of representation of the temporal monocular crescent, we were unable to identify it on any qualitative morphological features in the 'stem of the calcarine sulcus' (Wiesel, Habel and Lam, 1974). In the adjoining peristriate cortex, however, the figures were the same as in other areas ($\simeq 110$) and qualitative examination readily shows this difference in the density of the cells in areas 17 and 18 (fig. 2).

For the corresponding areas of the cortex in the brains of other species the counts were all remarkably similar, both within and between species (Table 3). In all species, except other primates, the figures for area 17 were the same as in other areas of the cortex. Within area 17 of the normal and Siamese cat there was no difference between the cortex containing the representation of the binocular and monocular parts of the visual field, nor between these and areas 18 and 19 and of the

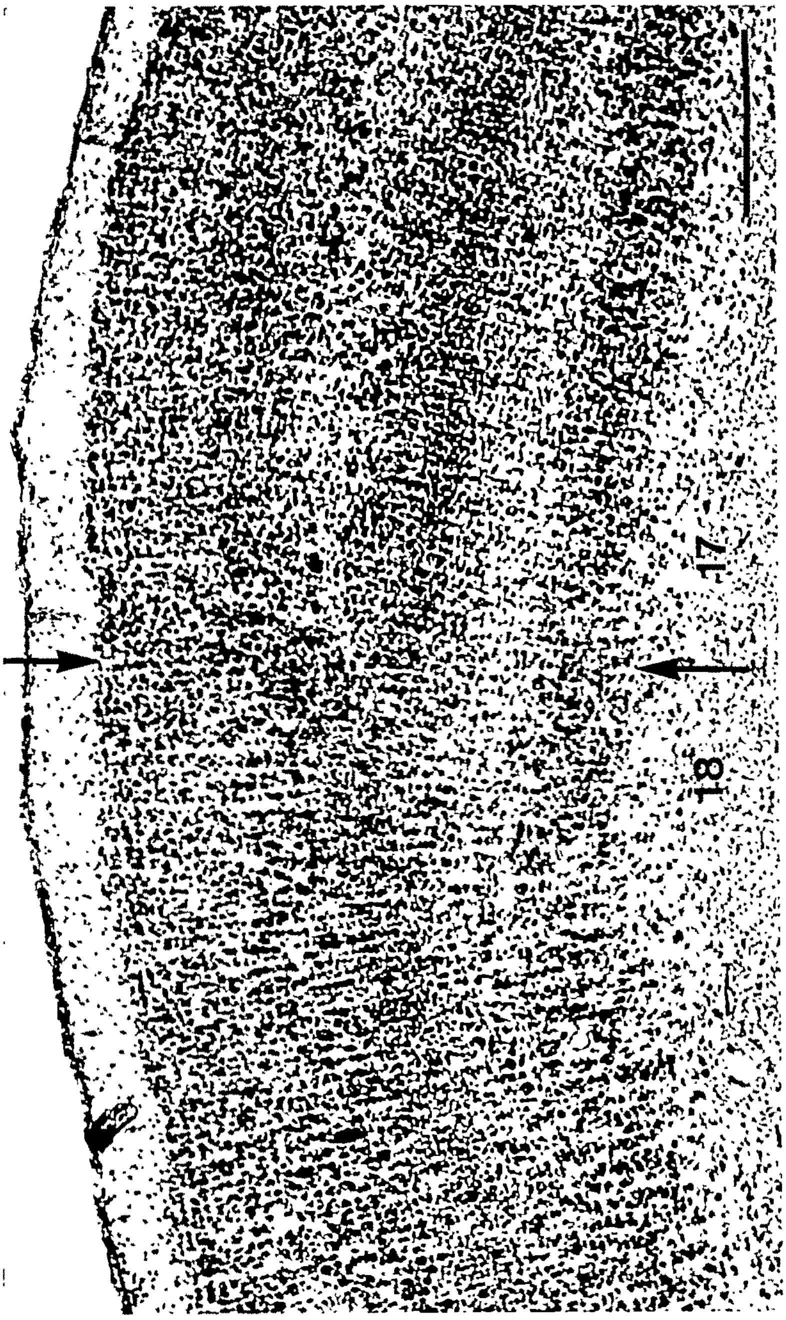


Fig. 2. The boundary between areas 17 and 18 in the macaque monkey; the greater density of neurons in area 17 as compared with area 18 is readily seen. Bar = 0.5 mm.

TABLE 3. COMPARISON OF CELL COUNTS

	Motor	*Somato-sensory*	*Frontal*	*Temporal*	*Parietal*	*Visual*	*Mean of means*
Mouse	109.2±6.7	111.9±6.9	110.8± 7.1	110.5± 6.5	104.7± 7.2	112.2± 6.0	109.9±6.8
Rat	108.2±5.8	107.0±6.7	104.3± 7.2	107.7± 9.2	105.2± 6.8	107.8± 7.9	106.7±7.4
Cat	103.9±7.6	106.6±7.2	108.0± 6.2	113.8± 7.3	110.6± 7.4	109.8± 9.9	108.8±7.7
Monkey	110.2±9.4	109.4±9.4	112.0±11.1	109.8±10.3	114.6± 9.9	267.9±13.7	—
Man	102.3±9.5	103 7±5.8	103.3± 8.6	107.7± 7.5	104.1±12.5	258.9±15.8	—

The mouse, rat, cat and man values are means of two samples of ten counts, one from each of two animals, in each area. The monkey values are based upon three animals, with two samples of twenty counts being made for each animal. The standard deviations shown are obtained from within animal pooled variances.

first auditory area of the cat. An analysis of variance was conducted with the 5 species (mouse, rat, cat, human and monkey) and the 5 areas (motor, somatosensory, frontal, temporal and parietal) being treated as fixed effects and two animals of each of the species being considered as random effects. The results show no significant differences between the species (F = 0.614; d.f. = 4,5) or between the areas (F = 1.75; d.f. = 4,470). A test for the human alone between the areas showed no difference (F = 0.64; d.f. = 4,4). Separate tests between all areas, *including the visual* as well as the five above, within the species indicates no difference in the rat (F = 1.06; d.f. = 5,5) and in the mouse (F = 3.63; d.f. = 5,5) but there is a suggestion of difference in the cat (F = 5.51; d.f. = 5,5; $P < 0.05$). The cells were more densely packed in the cortex of the smaller brains of the mouse and rat, and were more widely dispersed in the larger brains and especially the human. In general the cells were somewhat smaller in the smaller brains than in the larger brains and in some areas, such as area 17, than in the cortex of area 4. In certain areas, for example, the motor cortex of the monkey and the auditory cortex of the cat, it was quite evident during the traverse through the cortex that one was following and counting a definite row or 'column' of cells.

The higher figure for the number of cells in area 17 of the macaque monkey led to a study of this area in certain other primates which were available (Table 4). In all of these examples (except Tupaia) a similar count to that of the macaque was obtained and statistical analysis of them showed no significant difference. In testing for difference between these primates, as only one animal of each species was used, the between animal variability was estimated from the three macaque monkeys. The between primates difference was not significant when compared to this assumed between animal variability (F = 1.47; d.f. = 5,8). The peristriate cortex of these animals had, like the macaque, the lower figure of approximately 110, the same as in other areas. One finding of interest was a distinct difference in the binocular and monocular parts of area 17 of Tupaia, where it was possible to sample them because they have been identified with anatomical and physiological techniques (Kaas, Hall, Killackey and Diamond, 1972). In the monocular region on the medial and callosal surfaces of the hemisphere it was the same as in other functional areas of all species, but in the binocular part on the dorsal surface of the hemisphere the number was higher and about midway between that in area 17 of the other primates and that in the other functional areas. This finding led to the comparison of the monocular and binocular parts of area 17 of the cat and attempts to identify the monocular area in the macaque monkey. The counts of area 17 of the human brain were checked repeatedly and further blocks taken.

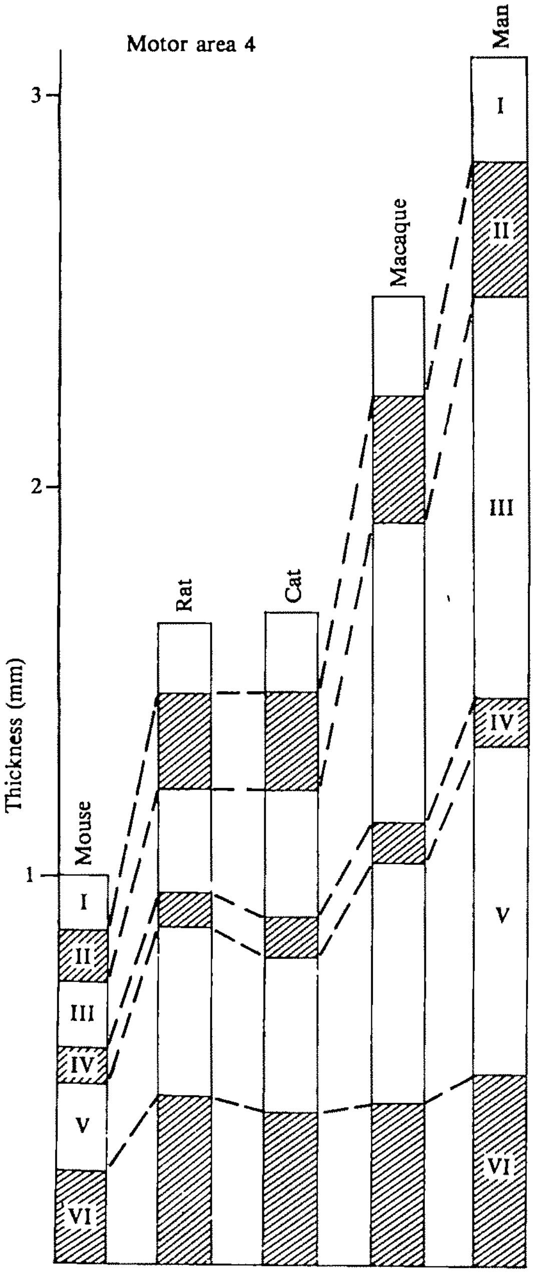
TABLE 4. MEAN AND SD OF COUNTS IN AREA 17 OF VISUAL CORTEX

Mouse	112.2 ± 6.0
Rat	107.8 ± 7.9
Cat	109.8 ± 9.9
Tupaia, Monocular	109.6 ± 9.19
Binocular	192.8 ± 8.40
Galago	277.40 ± 8.40
Marmoset	277.00 ± 9.65
Squirrel monkey	273.60 ± 13.16
Macaque	267.9 ± 13.7
Baboon	268.4 ± 7.2
Chimpanzee	279.00 ± 5.66
Man	258.9 ± 15.8

The thickness of the cortex and of the individual laminæ of certain functional areas in several brains (in the same sections as were used for the cell counts) were drawn with a drawing apparatus and a comparison of these (figs. 3–6) indicates the relatively small degree of difference in the cortex as a whole between mouse and man. In the motor and parietal cortex the increase occurs mainly in the supra- and infra-granular layers and in area 17 in layers III and IV. Within the non-human primates the thickness of area 17 is essentially the same in brains which varied in size from Tupaia to chimpanzee, but layer IV progressively thickens in the larger brains.

DISCUSSION

The major finding of this quantitative study of the neocortex has been the consistency of the absolute number of nerve cells in a strip of constant width through the entire thickness of the cortex from the pial surface to the white matter in several quite distinct structural and functional areas, both within the brain of one species and also in the brains of animals as widely different in size as mouse and man. The only exception to this similarity is the binocular part of area 17 of the visual cortex in a number of primate brains, in which there are approximately 2.5 times as many neurons. It would seem that in evolution the *number* of cells in the thickness of the neocortex, and thus underlying unit area of cortical surface, of the mammalian brain has remained constant, except in area 17 of certain primates where it has increased considerably. A width of 30 μm within which to count the cells was chosen partly because of the evidence suggesting that this is approximately the width of the simplest functional column in the neocortex (Welt, Aschoff, Kameda and Brooks, 1967; Hubel and Wiesel, 1974), and the number of cells found in it would therefore represent one quantitative feature of the anatomical basis of the



FIGS. 3-5. The change in thickness of the cortex in the motor, parietal and visual areas between mouse and man.

functional column. As well as being the functional unit of the cortex the findings suggest that the column may also be a morphological and developmental unit. The thickness of the neocortex does vary between different areas within the same brain and between corresponding areas of different brains, and in the latter case it is due to variations in thickness of certain laminæ, the particular laminæ involved depending upon the function and connections of the cortical area.

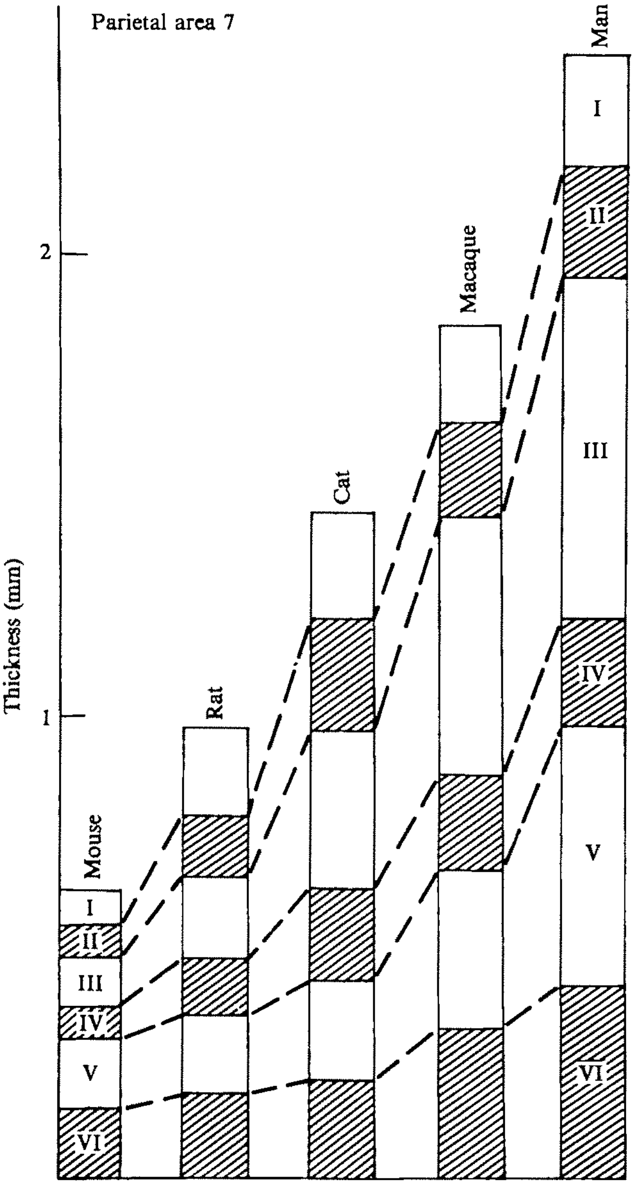


FIG. 4

The number of cells in the cortex of different areas and brains may indeed be identical, and certainly the size of the standard error for the mean number over the whole sample (except for area 17 in primates) would not contradict this hypothesis. The slight variations which have been found could have been due to technical factors such as the occasional inclusion of a glial cell, omission of some nerve cells in lightly stained sections, some blocks not being cut strictly perpendicular to the surface, or the sampling traverse not passing perpendicularly; the boundary between grey and white matter is not sharp in some areas so all the cells may not have been included. With one exception, area 17 of the human brain, counts of

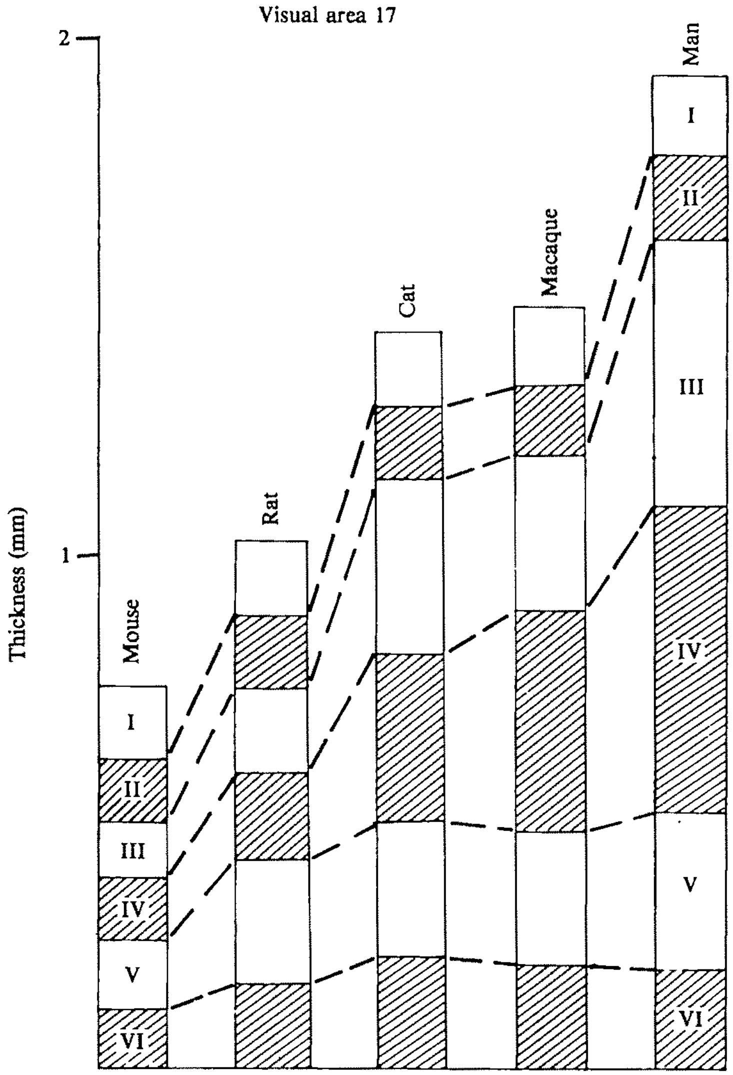


FIG. 5

all areas repeated after an interval of some years showed no significant difference. In contrast to the other primate brains it had been found earlier that there was a significantly lower number of cells in area 17 of the human, but as this finding was difficult to interpret counts were repeated and further blocks and sections cut. When it was realized that the low figures might have been due to many of the small cells not being adequately stained, probably due to imperfect fixation, the coverslips on the slides were removed and the sections were restained deeply; the number of cells was then found to be almost as high as in other primates, but in these restained sections the figure in the peristriate cortex was still approximately 110. In the visual cortex of the two human brains Cragg (1967) studied, the density of cells in area 17 in one brain was approximately half that in the other, and although he could offer no explanation it might have been for the same reason. One finding which was initially a marked discrepancy actually provided support for the validity of the counts. In one macaque monkey brain (not included in Table 1) the counts of area 17 were about 170 instead of around 270, and this was disturbing until it was

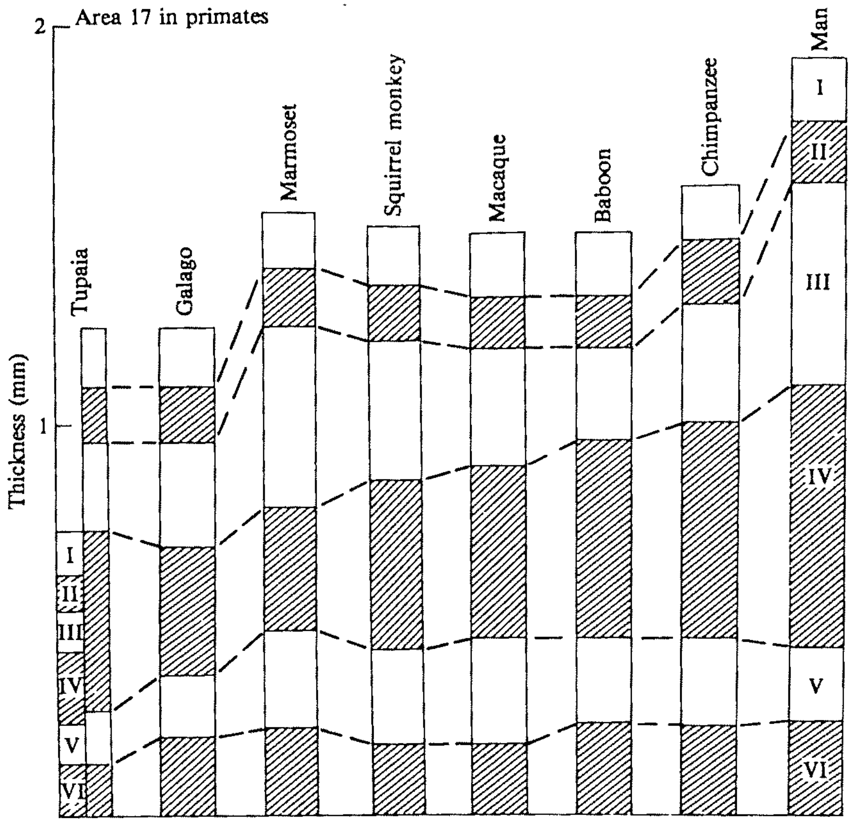


FIG. 6. The thickness of the cortex of area 17 in several primates; in Tupaia, in which it was possible to measure the monocular and binocular regions, the monocular (*left*) is approximately half the thickness of the binocular (*right*).

found that the sections had been cut at a thickness of 15 μm rather than 25 μm; in the thinner sections this was the figure one should have obtained. The actual figures obtained in counts of cells through the thickness of the cortex may vary with different methods of fixation and histological processing, and if the sections are not cut strictly perpendicular to the surface increasing angles of obliquity would result in the cortex being thicker and the counts greater.

In a study of ageing in the cerebral cortex Brody (1955) counted the cells through the thickness of the cortex in a much wider strip (1125 μm) and in thinner (10 μm) sections than in the present study in several areas in many brains. Analysis of his data shows that he found the number of cells to be the same in the adult pre- and post-central and inferior temporal gyri, but almost twice the number in the superior temporal and striate cortex. From the figures provided by Brody one can calculate that in the volume sampled in the present study he would have counted 80 to 90 cells in the pre- and post-central and inferior temporal gyri. If allowance is made for several differences in methodology the figures are in good agreement with ours and indicate that sampling a wide strip of cortex would not alter our conclusion about the constancy of cell numbers in different areas.

An exception to the similarity in absolute number in the different areas and species was area 17 of the primates, and a much higher density of neurons in primate visual cortex than in several non-primate brains was also found and discussed by Cragg (1967). In all brains the figures for the adjoining peristriate cortex of areas 18 and 19 were the same as in other functional areas, $\simeq$ 110. In the visual cortex of Tupaia the binocular part had a number that was midway between the high figure characteristic of area 17 of the other primates and that of the other species, but the monocular area was the same as in other functional areas. It was not possible to identify the region of representation of the monocular segment in the other primate brains, so it is not known whether the increase in number of cells occurs only in the binocular part. In view of the difference found in Tupaia it is obviously important to count the cells in primates in which the monocular segment is clearly identifiable after injection of labelled amino acids into the eye (Wiesel *et al.*, 1974). Until this has been done one can only speculate about the functional significance of the increase in number of cells in area 17 of primates, but it may be significant that in the binocular part of Tupaia, in which the number of cells is midway between that of area 17 of other primates and of the other functional areas of all animals, the projection of the different laminæ of the lateral geniculate nucleus (related to different eyes) is upon different laminæ rather than to adjoining columns as in the macaque (Harting, Diamond and Hall, 1973; Casagrande and Harting, 1975; Hubel, 1975). The larger number would not appear to be related solely to a pronounced ocular dominance columnar arrangement, however, because the same number of cells has been found in area 17 of squirrel and macaque monkeys in this and a previous study (Cowey, 1964) but ocular dominance columns have not been shown with histological techniques in the squirrel monkey (Hubel and Wiesel, 1977; Hendrickson, Wilson and Ogren, 1978). Whatever the explanation proves to be, it may be noted that information about an individual stimulus coming through two eyes and two pathways is first brought together in area 17, and the relative size of the uncrossed pathway increases in phylogeny.

The large number of cells in area 17 of the primate, in which vision is probably the most important and dominant sensory pathway, raises the possibility that there may be more cells in other 'specialized areas' such as the supratemporal plane and Broca's area in the human brain, the auditory cortex of echo-locating bats and the barrel fields related to the vibrissæ in certain rodents. That this may indeed be so is suggested by the figure for the cortex of the human superior temporal gyrus in Brody's (1955) study being higher than in other areas (except area 17).

In the electron microscopic study of the motor and somatic sensory areas of the monkey the proportions of pyramidal and non-pyramidal cells, as identified on the ultrastructural features of their cell somata, were found to be the same, as well as the absolute number of neurons (Sloper, 1973; Sloper *et al.*, 1979). Similar proportions have been found in area 17 of the monkey (Tömböl, 1974), in the visual and motor areas of the rat and cat (Winfield, Gatter and Powell, 1980) and in human temporal cortex (unpublished observations). Although the proportions of the two major types of cells in the cortex remain constant, their laminar distribution may vary, as has been found between the motor and somatic sensory areas of the monkey (Sloper *et al.*, 1979).

The pattern of distribution of the intrinsic cortical connections is also essentially similar in areas of the monkey as different in cytoarchitecture and function as area 17 (Fisken, Garey and Powell, 1975), the motor cortex (Gatter and Powell, 1978), the somatic sensory area and area 5 (Shanks, Pearson and Powell, 1978; Vogt and Pandya, 1978). Several studies with retrograde axonal transport methods have shown that with few exceptions the laminar origin of the efferent fibres from the cortex is similar in most areas, the cortico-cortical arising mainly from layer III but with some from layer V, the cortico-thalamic from layer VI and those to other subcortical sites from layer V (*see* Gilbert and Kelly, 1975; Lund, Lund, Hendrickson, Bunt and Fuchs, 1975; Jones and Wise, 1977). These findings of a basic uniformity in structure of the cortex are apparently in contrast to the differences in cytoarchitecture between areas and they raise the question of the cause of the differences in morphology that are readily seen between the motor, sensory and association areas. The apparent contradiction may be resolved if one considers that the absolute numbers and proportions of the main cell types are constant and that the pattern of intrinsic fibre connections is essentially uniform throughout the neocortex, but the morphological differences which form the basis for cytoarchitectonic differentiation are correlated with variations in the relative sizes of the major afferent and efferent fibre pathways of individual areas, and particularly the relative proportions of cortico-cortical connections compared to those with subcortical structures. Certain architectonic features are, however, due to differences in intrinsic structure of the cortex; in area 17 of primates there are more cells and the accentuation of the outer band of Baillarger into the prominent stria of Gennari probably results from the greater number of non-pyramidal interneurons.

Many studies with a variety of techniques in recent years have shown that variations in connections are present, that the changes in density of the afferent or efferent pathways occur precisely at architectonic boundaries and that correlations can be made between the relative strength of the connections and cytoarchitecture. The extensive literature will not be reviewed but only the more relevant findings and mainly from the monkey will be considered (*cf.* Powell, 1973; Jones and Burton, 1976). The granular or koniocortex of the sensory areas receives a large number of fibres from the thalamus and the number and size of these diminish abruptly at their limits. Marked variations in the size of the thalamic projection have been found between several areas of the parieto-temporal lobe and again the changes coincide with boundaries determined on morphological criteria (Jones and Burton, 1976). The number of afferent and efferent cortico-cortical fibres also varies considerably, the koniocortex of area 17 and of area 3b having few but the adjoining peristriate areas and areas 1 and 2 of the somatic sensory area, together with the association areas, having far more. There is increasing evidence to indicate that thalamo- and cortico-cortical fibres terminate in narrow bands of cortex (*cf.* Hubel and Wiesel, 1977; Imig and Brugge, 1978; Shanks *et al.*, 1978), and the latter are often situated at boundaries of architectonic areas which may have clearly distinguishable morphological features. In the subdivisions of the visual (Zeki, 1977) and somatic sensory areas (Shanks *et al.*, 1978) the parts of the cortex of one hemisphere which have commissural connections are connected with each other by association fibres and regions devoid of commissural connections only with other non-commissural parts; in the auditory cortex a similar principle seems to be present as both commissural and association connections are present throughout most of the individual subdivisions (Diamond, Jones and Powell, 1968*a*, *b*; Pandya, Hallett and Mukherjee, 1969). The change in strength of the various afferent and efferent pathways which coincides with architectonic boundaries is associated with differences in the laminar termination of afferent fibres, with the demarcation and degree of development of individual laminæ and with the arrangement of the cells in rows or columns. When the thalamic pathway is strong the fibres end mainly in layer IV, but as the number of thalamic fibres progressively diminishes their termination becomes more restricted to layer III (Jones and Burton, 1976). Although cortico-cortical fibres terminate in all layers, when these increase to form the major afferent pathway to a particular area most of them terminate in layer IV (Martinez-Millán and Holländer, 1975; Pearson and Powell, 1978). Thus layer IV appears to be the major site of termination of the strongest afferent pathway to any individual area. The cortico-cortical fibres arise mainly from layer III and in areas which send many cortico-cortical connections this layer is more prominent with larger and more widely spaced pyramidal cells. The degree of columnar arrangement of the cells in any cortical area is a reflection of the number of cortico-cortical connections as these fibres run perpendicular to the surface, with the efferent fibres from layer III passing deeply through the other layers and the afferent fibres ascending through most layers. In areas of the cortex in which early descriptions emphasized the columnar arrangement of cells, recent work has shown that there are strong cortico-cortical connections. This is true of the koniocortex of the auditory area which has numerous commissural and association connections in contrast to the koniocortex of area 3 of the somatic sensory area and area 17 of the visual cortex, both of which have few cortico-cortical connections and little columnar arrangement; the increasing columnar arrangement as one moves from the koniocortex of areas 17 or 3b into adjoining areas can be explained on the same basis.

The significance of recent observations on the origin and termination of connections with other cortical and sub-cortical sites in narrow bands or columns, and the fact that subcortical sites such as the amygdala, basal nucleus and locus coeruleus are sending fibres to the cortex, is not clear. Further studies with more refined methods will show an even greater complexity but on the present evidence some general conclusions may be drawn. The heavier the afferent pathway is from the thalamus *and* the sparser the cortico-cortical connections, the cytoarchitecture is that of the granular or koniocortex as typified by area 17 and area 3b and the granular barrel fields of the somatic sensory area of certain rodents (Woolsey and Van der Loos, 1970; Welker, 1976). Here, layers II, III and IV are difficult to distinguish and there is little arrangement of the cells in columns. In the koniocortex of the auditory area, where there are more cortico-cortical fibres, layer III is prominent and there is a columnar arrangement of the cells. In other subdivisions of the sensory areas where the thalamic afferents are sparser *and* the cortico-cortical fibres increase, layer III has larger pyramidal cells and is more clearly demarcated together with the cells becoming columnar in arrangement. Although area 4 also has a strong afferent pathway from the thalamus the dominant cytoarchitectural feature is the greater size of the pyramidal cells in layers III and V, correlated with the widespread efferent projections to cortex and subcortical sites by larger or longer axons or more axon branching. The clear lamination of the homotypical association cortex probably reflects a more even balance between the various afferent and efferent projections. There are complex interrelationships between the proportions of the several diverse afferent and efferent pathways so the cytoarchitectural changes may occur in gradients. The greater differences in relative proportions between the pathways to certain areas in larger brains may underlie the clearer architectonic differentiation; in the thalamic connections of the subdivisions of the somatic sensory and visual areas definite differences are found between the cat and monkey (Wilson and Cragg, 1967; Jones and Powell, 1970; Hendrickson *et al.*, 1978). The differences in architecture found in the neocortex are mainly due to these variations in the density of connections, changes in cytoarchitecture being accompanied by changes in connections.

A cytoarchitectonic area can be defined not only on the basis of its intrinsic cellular structure but also as one having the same pattern of afferent and efferent connections and the same function throughout, the only difference within it being related to topographical representation. The functions of individual areas are dependent upon their connections, and differences in the origin and termination of these, and of the ratios between them, determine the differences in function that have been shown between architectonic areas; the number and proportions of the neurons remain constant. Although the proportions of the pyramidal and non-pyramidal neurons are the same in areas as diverse as the motor and somatic sensory, the details of the form of the cells need not be identical, because the dendritic ramifications, density of axonal arborization and the layers of termination of the afferent pathway may vary. It is impressive, however, how similar are the descriptions of the types of Golgi-impregnated neurons in different areas and species (*cf.* Lorente de Nó, 1949; Jones, 1975; Feldman and Peters, 1978).

The variations in density between the various pathways which underlie cytoarchitecture may be governed by certain principles determining the interrelations between the proportions, the origin and the termination of the different connections. There is, for example, the reciprocity in origin and termination of most commissural connections, the relationship of the commissural and non-commissurally connected regions in the same hemisphere to each other, a possible complementarity between strength of the thalamo-cortical and cortico-cortical connections of any individual area, and a reciprocal relationship in the strength of thalamo-cortical and cortico-thalamic pathways. If all pyramidal cells send their axons into the white matter, and non-pyramidal do not, the total number of efferents is the same from each unit cylinder through the depth of the cortex (except area 17 in primates) because the total number of cells and the proportion of pyramidal cells remain constant, and there must therefore be an interrelationship between the proportions of the efferent fibres to different sites. Whether there is also a similar relationship in the afferent connections must remain speculative, but the available evidence is suggestive.

The thickness of the cortex does not vary much between brains of different sizes and the figures show that even in the motor cortex there is barely a three-fold increase between mouse and man. In the motor and parietal areas the major increment is in layers III and V, which are the main sites of origin of the efferent fibres, and the apical dendrites of the pyramidal cells will become longer. In the visual cortex layers III and IV show the greatest increase, but within the primates it is surprising how little change there is in total thickness between Tupaia and Man. The obvious change that does occur in the cortex with increase in size of the brain is increase in its *area. From the findings of the constancy in number and proportions of cell types in the cortex between different areas and species it seems probable that early in mammalian evolution these two quantitative features of the cortex are determined genetically and this specification remains constant. It may be that the number of cells through the depth of the cortex is not specified directly, but rather the specification is for a constant packing density for cells in the horizontal plane, that is when projected upon the cortical surface in the mature brain* (figs. 7 and 8).

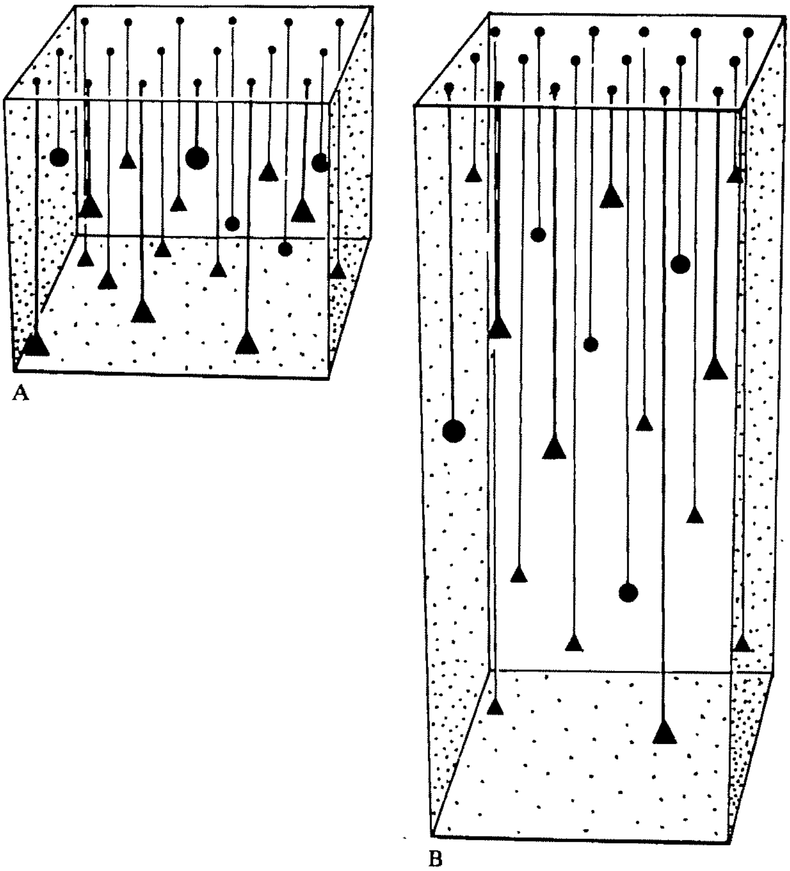


FIG. 7. Schematic figure of mature cortex to illustrate the same number of neurons through the depth of the cortex, and constant packing density when projected upon the surface, in the cortex (A) of small brains (mouse or rat) and in thicker cortex (B) of larger primate brains. Pyramidal (▲) and stellate (●) cells retain the same proportions in different species. The lines extending vertically from the cells to the surface are projection lines, and in the case of pyramidal cells they could also represent the apical dendrites.

This constancy in number of cells (and proportions) through the depth of the cortex may be an expression of a basic structural and functional unit or module. Although the volume of the cylinder of cortex that was sampled in this study is approximately the size of the smallest functional column (Welt *et al.*, 1967; Hubel and Wiesel, 1974) it should be emphasized that this is not necessarily the size of the simplest anatomical unit. In the cortex of larger brains the number of these units or modules increases, by repeated specification, and the additional ones are assembled side by side. The increase in the number of modules would be accompanied by a corresponding increase in the interconnections between themselves and other parts of the central nervous system. In the neocortex of primate brains the increase in number of modules occurs particularly in the association areas

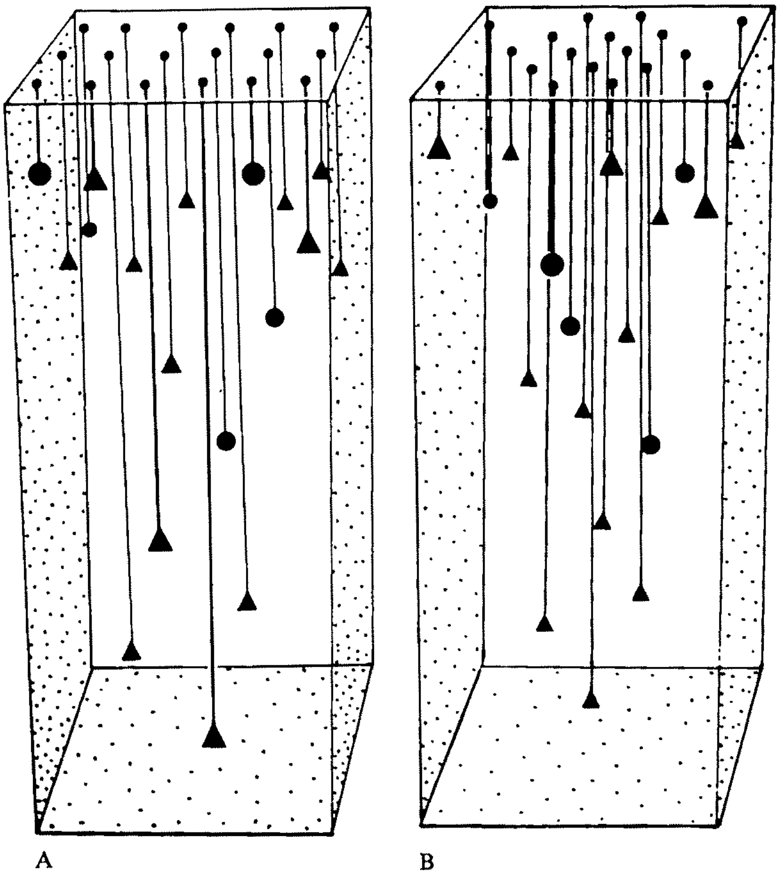


FIG. 8. Schematic figure to show that when the cells in the cortex are arranged in 'columns', as in the auditory cortex or in area 4 in primates, the packing density when projected upon the surface remains constant (as in fig. 7) and it could either be uniform (A) or there could be local variations within the same overall density (B). The much greater density of cells actually present in the cortex than in the figures would accentuate the appearance of a columnar arrangement.

of the frontal and parieto-temporal lobes and it is significant that in these areas the increase in thickness of the cortex is predominantly in layers III and V which are the source of intracortical connections. Increase in area, but not in thickness or number of cells through the depth of the cortex with increase in size of the brain, has been shown to be true for area 17; the thickness of the cortex and the number of cells through its depth are the same in squirrel and macaque monkeys, but the area is twice as great in the macaque (Cowey, 1964). The greater thickness of the cortex and vertical spacing of the cells in the larger brains is no doubt due largely to the more numerous and extensive dendritic and axonal ramifications because with an increase in area of cortex by one square centimetre there will be several million more cells and axons, many of which are terminating within the cortex either in the immediate vicinity or in other areas of the same or opposite hemispheres. The uniformity of structure and function throughout the binocular part of area 17 in the monkey has been emphasized by Hubel and Wiesel (1977), and they have concluded that the same basic units are present throughout but more of them 'are used per degree of visual field the greater the detail of analysis'. These authors have also pointed out the advantages in development of such uniformity of structure with replication of the same specification. From the present data and the evidence of the pattern of intrinsic connections, it is suggested that essentially the same structural units are present throughout the whole of the neocortex. The differences in function between cytoarchitectonic areas depend upon differences in the total pattern of connections of these modules, and increases in number of modules within a particular functional area, or between areas and species, will be an accurate reflection of the greater analysis of detail and of the functional importance of that region. Preliminary counts of areas of the cerebral cortex other than the neocortex (pyriform, hippocampal) suggest that although the absolute number of cells in individual areas is different from that of the neocortex and from each other there is the same constancy in the absolute number in the same structure between different species.

The width of 30 μm within which the cells have been counted is of the same order of size as the smallest functional column in the cortex where it has been possible to measure them (Welt *et al.*, 1967; Hubel and Wiesel, 1974). Whether this indicates more than a chance association and that the absolute number of cells found here form a structural and functional unit (together with their connections), the basis of the functional column, must remain conjectural until more is known of the intrinsic synaptic organization of the cortex. The presence of a columnar functional organization in all areas of the neocortex that have so far been investigated (Mountcastle, 1978), however, is in accord with the basic uniformity of structure of the neocortex that has been suggested here. The significance of the columnar organization is in the processing of incoming information, vertically within a column and horizontally between adjoining columns, with a wide and diverse distribution of the results through the numerous pyramidal cell axons; the form of the processing might be essentially similar in all areas but the differences in function between areas would be due to the differences in the *sources and termination* of their connections.

The constancy of the number of cells that is present through the depth of the cortex in different areas irrespective of the variation in thickness of the cortex should permit accurate assessments of the number of cells in the whole cerebral cortex after its surface area has been determined (Mountcastle, 1978). For such estimates a correction factor for shrinkage must be used, *both* for the total surface area and for the number of cells in fixed tissue; in the present study (Material and Methods) it has been found that for the sections of human brains the linear shrinkage was of the order of 18 per cent. If the conclusion about the correlation of cytoarchitectural differentiation with connections is correct, emphasis should be placed upon the more objective results of investigations in which the total pattern of connections of areas of the cortex are determined rather than upon the still somewhat subjective criteria of cytoarchitecture. This suggestion would apply particularly to the association cortex of the frontal and parieto-temporal lobes, where rigorous physiological studies are now making progress. It may also be worth investigating whether there are changes in the number or proportion of cells *through the depth* of the cortex in the brains of animals and patients with disorders of known genetic basis. In several mutant strains of mice genetically associated variability in numbers of neurons has been found in all regions of the hippocampus (Wimer, Wimer, Vaughn, Barber, Belvanz and Chernow, 1976), and in the dentate gyrus the total number of cells varies in different strains (Wimer, Wimer, Vaughn, Barber, Belvanz and Chernow, 1978), being severely reduced in the reeler mouse (Stanfield and Cowan, 1979). There is a common genetic specification for cell number throughout the entire granule cell lamina of the dentate gyrus (Wimer *et al.*, 1978) and the effects of mutation upon the structure of the hippocampus appear to be only in the radial dimension (Stanfield and Cowan, 1979). These observations are in accord with our hypothesis that the number of cells through the depth of the cortex (or the constancy in packing density of cells as projected upon the surface) is determined genetically, and in mutant strains of animals and in human patients with genetic disorders this parameter of cortical development may be selectively affected.

SUMMARY

The number of neuronal cell bodies has been counted in a narrow strip (30 μm) through the depth of the neocortex in several different functional areas (motor, somatic sensory, area 17, frontal, parietal and temporal and in many species (mouse, rat, cat, monkey and man). With the exception of area 17 of the visual cortex in a number of primates the same absolute number ($\simeq$ 110) of neurons has been found in all areas and in all species. In the binocular part of area 17 of the primates there are approximately 2.5 times more neurons. Thus in mammalian evolution the area of the neocortex increases in larger brains but the number of neurons through the depth remains constant, except in area 17 of primates. From these and other findings it is suggested that the intrinsic structure of the neocortex is basically more uniform than has been thought and that differences in cytoarchitecture and function reflect differences in connections.

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AN ELECTRON MICROSCOPIC STUDY OF THE TYPES AND PROPORTIONS OF NEURONS IN THE CORTEX OF THE MOTOR AND VISUAL AREAS OF THE CAT AND RAT

by D. A. WINFIELD, K. C. GATTER *and* T. P. S. POWELL

(*From the Department of Human Anatomy, University of Oxford, South Parks Road, Oxford*)

INTRODUCTION

Two main types of neurons have been identified with the electron microscope in the mammalian cerebral cortex: the pyramidal and the non-pyramidal neurons (Colonnier, 1968; Jones and Powell, 1970; Peters and Kaiserman-Abramof, 1970; Peters, 1971; Garey, 1971). Recent investigations of the motor, somatic sensory and visual areas of the cerebral cortex of the monkey (Sloper, 1973; Tömböl, 1974; Sloper, Hiorns and Powell, 1979) have shown that the non-pyramidal cells may be subdivided into large and small stellate groups and that despite the differences in function and cytoarchitecture of these cortical areas the proportions of these types of neurons are remarkably similar. In view of the constancy in the proportions of these neuronal types in such different cortical areas of a single species, it was thought of interest to determine whether their relative proportions were similar in corresponding areas of the cortex of other mammals. In this study the cell somata have been examined in the motor and visual areas of the cat and rat.

MATERIAL AND METHODS

The material was taken from the binocular part of area 17 and from area 4 of two normal cats and from areas 17 and 4 of three normal rats; a block was also taken from area 17 of the visual cortex of one normal monkey in order to provide a direct comparison with the earlier results of Tömböl (1974) on this area and to provide a check that the criteria used in the present investigation were the same as those used in the previous studies on the monkey. The animals were anæsthetized and under hypothermia were perfused through the left ventricle of the heart with buffered saline and a mixture of 1 per cent glutaraldehyde and 4 per cent formaldehyde. The brains were removed and immersed for a period in the same aldehyde mixture. The blocks of the cortex were approximately 1 mm square cross-section and extended through its depth. In the monkey they were taken from that part of area 17 on the exposed lateral surface of the hemisphere. In the cat, blocks of area 17 were cut from the medial surface of the hemisphere close to the suprasplenial sulcus at the level of the junction of the lateral and post-lateral sulci, and blocks of area 4 were taken from the middle of the dorsoventral extent of the posterior wall of the cruciate sulcus after the anterior third of the hemisphere had been cut sagittally into slices of a few millimetre thickness (*see* Hassler and Muhs-Clement, 1964). In the rat, blocks of area 4 were taken from coronal slices of the hemisphere at a level known from other studies, and this was confirmed by examining the 'thick' section for the presence of Betz cells in layer V; blocks of area 17 were obtained from the middle of this area in the posterior third of the hemisphere. The blocks were post-fixed in osmic acid, washed in sucrose buffer, dehydrated in ascending alcohols (being stained at 70 per cent with uranyl acetate) and embedded in Epon-Araldite. One micrometre 'thick' sections for light microscopy were cut from the long face of the blocks and stained by the method of Richardson, Jarrett and Finke (1960). Ultra-thin sections perpendicular to the pial surface and extending through the whole depth of the cortex were then cut, mounted on Formvar-coated 1 × 2 mm single hole grids and stained with uranyl acetate and lead citrate. Every cell throughout the depth of the cortex which received a synapse and was cut centrally, as judged by the size of the nucleus and the lack of nuclear pores seen face on, was examined carefully and photographed in a series of equal width strips through the cortical depth. In the cat and rat four strips were sufficient to provide a sample of about 100 cells, and in the monkey only two similar widths were required.

From the photographs the number of synapses upon the cell somata of each class of neuron have been obtained in order to compare the functional areas and the species according to the distributions of synapses on the somata.

RESULTS

With the electron microscope it has been possible to distinguish in the visual and motor areas of the cortex of the rat and cat the classes of neurons previously described in the motor, somatic sensory and visual areas of the monkey (Sloper, 1973; Sloper *et al.*, 1979; Tömböl, 1974). The ultrastructural features and laminar distribution of pyramidal cells are in close agreement with the previous descriptions (Colonnier, 1968; Jones and Powell, 1970; Peters and Kaiserman-Abramof, 1970; Garey, 1971). Perikarya of pyramidal cells are usually triangular in shape with an apical dendrite directed towards the pia, and have only symmetric synapses on the cell surfaces (fig. 1). They occur in all layers except layer I, and although they vary considerably in size their internal structure is constant throughout the depth of the cortex. The large nucleus commonly has a small indentation of its membranes and sections taken through the edge of such nuclei suggest that, although narrow and never penetrating deeply into the nucleus, this indentation runs along one of its sides. In the cytoplasm rosettes of free ribosomes are especially prominent. Rough surfaced endoplasmic reticulum is widespread, though not densely concentrated, normally appearing as one or two cisternæ at regular intervals and other organelles, typical of all neurons, are also present. Large Meynert (Chan-Palay, Palay and Billings-Gagliardi, 1974) and Betz (Kaiserman-Abramof and Peters, 1972; Sloper *et al.*, 1979) cells have been recognized in the visual and motor areas, respectively. The cell bodies of these neurons are large and triangular in outline, have abundant granular endoplasmic reticulum and organelles in their cytoplasm and a relatively high number of synapses upon their surfaces. These were the largest cells present and have been included with the pyramidal cells in the quantitative studies.

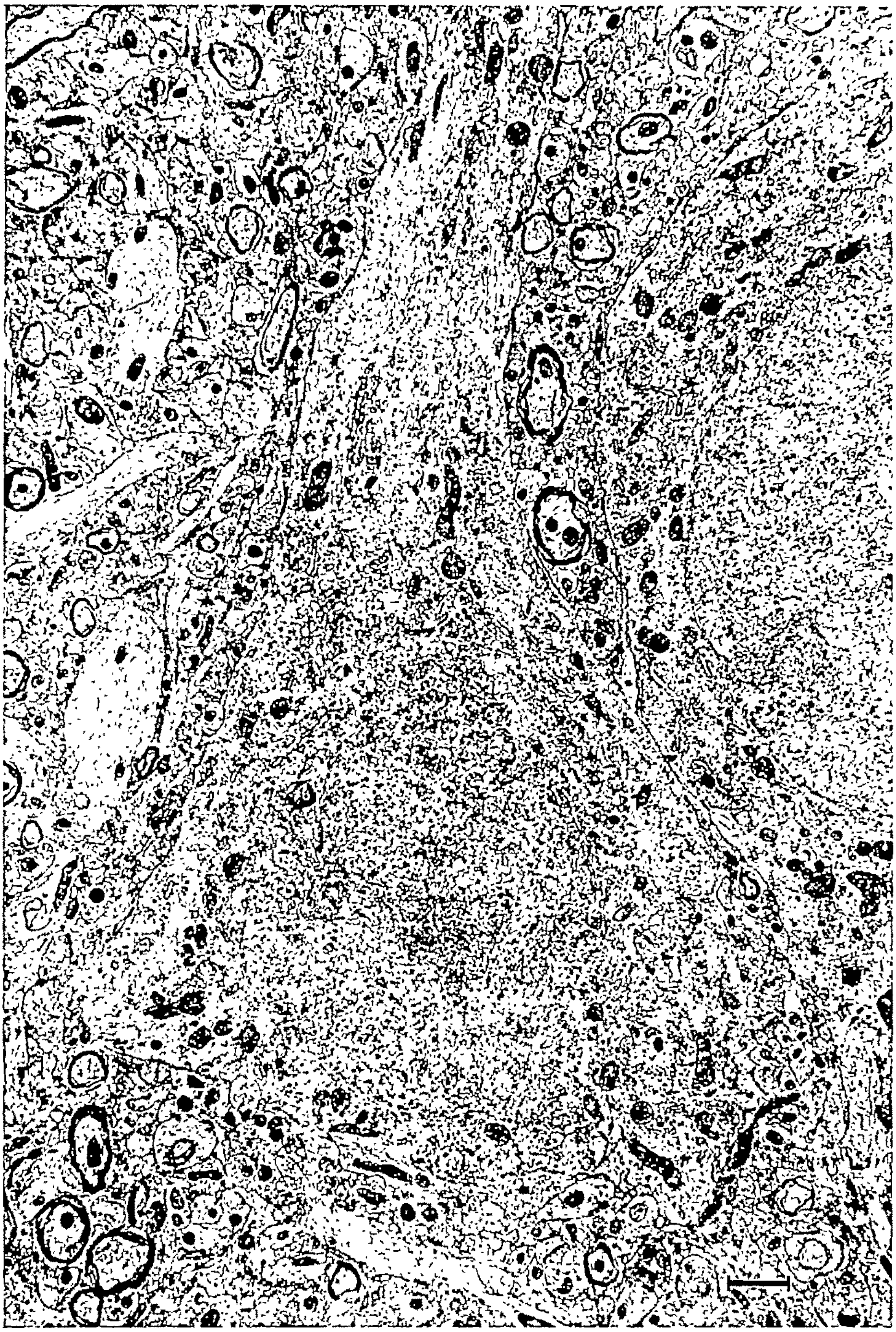

FIG. 1. Pyramidal cell from the visual cortex of the rat showing the typical triangular outline and apical dendrite directed toward the pial surface. Bar = 2 μm.

Of the non-pyramidal neurons some are readily recognizable (fig. 2) as they correspond closely to previous descriptions of typical stellate cells in the neocortex (*see* Colonnier, 1968; Jones and Powell, 1970; Peters, 1971). They have abundant cytoplasm, with many organelles, particularly mitochondria, and numerous synapses of both types on the somata; they are present in the lower half of layer III and the deeper layers. The mean diameter in the visual cortex was 14 μm in the rat, 18 μm in the cat and 13 μm in the monkey. Many other non-pyramidal cells are present and can be distinguished by their smaller size *and* several other features. They are round or oval with sparse cytoplasm and with far fewer synapses on them (figs. 3 and 4); in the visual cortex of the three species the mean diameter was 10 μm. The outline of the nucleus is quite irregular, with a number of indentations, but the 'clumping' of nuclear chromatin, which is a feature of these cells in the monkey, is not so constant or marked in the cat or rat. These cells may resemble small pyramidal cells in sections that miss the apical dendrite, but unlike pyramidal cells which have only symmetric synapses upon their cell somata, they have *both* symmetric and asymmetric synapses. The number of synapses upon the cell body per section is usually small, one or two asymmetric and symmetric, but up to five have been seen. The smaller cells are found in all laminæ but are concentrated in layer IV. They are frequently in groups of two to four, and within the groups parts of the plasma membranes may be closely apposed but with no specialized ultrastructural features. Some of the cell bodies have a small sessile spine which receives an asymmetric type synapse. Although the majority of these cells are round or oval, a small number are elongated with a deep nuclear indentation, closely resembling the type of neuron described as fusiform by Sloper (1973) and Tömböl (1974). The fusiform type is seen most frequently in the deeper layers but is present in all layers except layer I. It is often situated close to a blood vessel with its long axis orientated either parallel or normal to the pial surface.

The results of the cell counts are shown in Table 1. Cells in the visual cortex of the monkey were counted as a control for the criteria which have been used for classification of neuron types in the rat and cat. The relative proportions of the cells in the different areas and in different species are of the same order of magnitude, approximately two-thirds of the neurons being pyramidal and of the non-pyramidal the small are the more numerous with the large forming less than 10 per cent of the total.

Although the three types of neurons occur in similar proportions in two different functional areas in the three species, differences are found when the numbers of synapses upon their somata are analysed. The mean numbers (Table 2) and distribution (fig. 5) of synapses upon both the pyramidal and small stellate cells of the motor (Sloper *et al.*, 1979) and visual areas are lower in the monkey than in the cat and rat. The pyramidal cells in the visual cortex of the monkey have 50 per cent less, which is significantly lower ($P < 0.001$) than in the cat or rat which are similar to each other. In the motor cortex of the monkey the pyramidal cells also have a lower mean number as compared with the cat and rat, but the difference

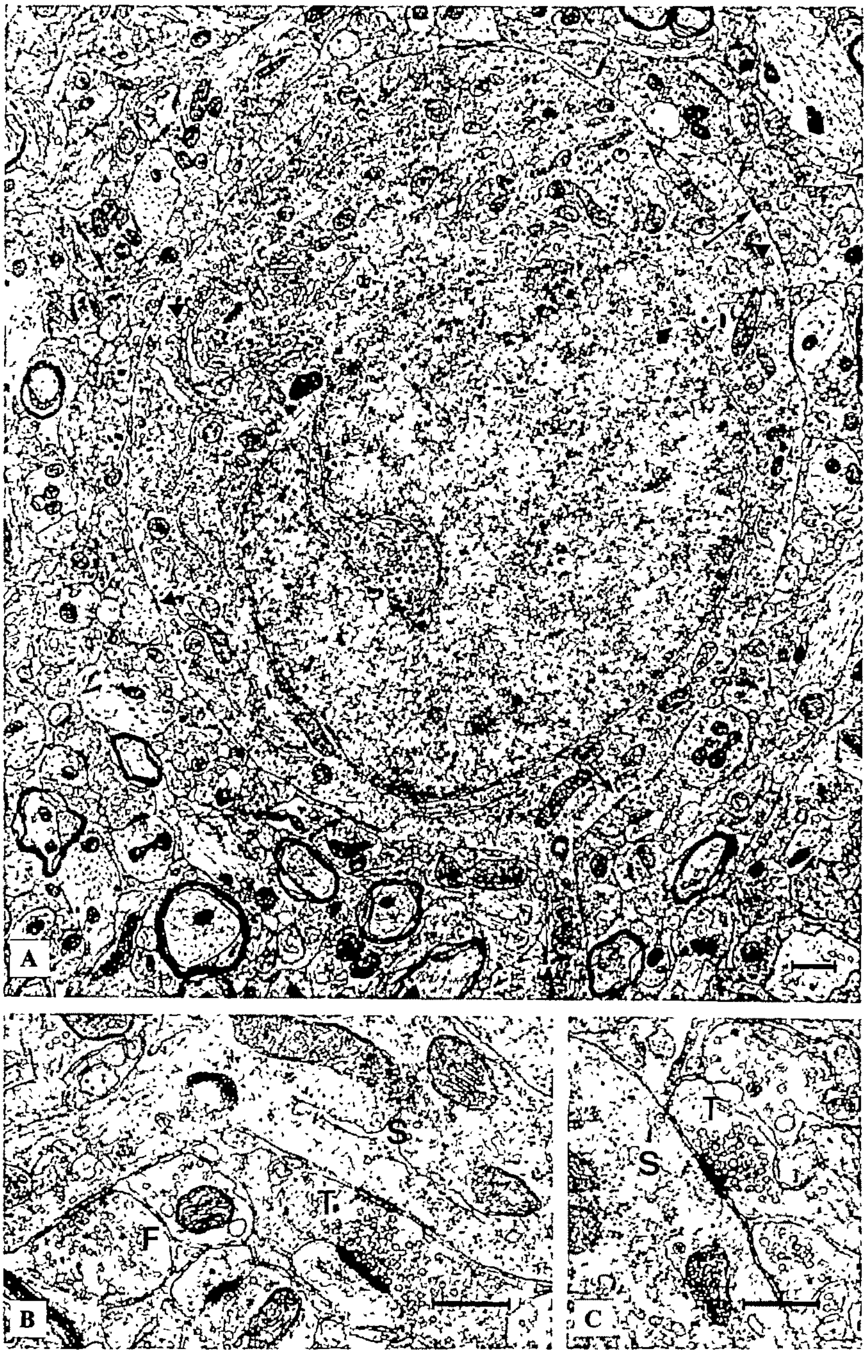

FIG. 2. A non-pyramidal cell of the large stellate class (A) from the visual cortex of the cat with abundant cytoplasmic organelles and numerous synaptic contacts upon the soma surface (arrows and arrowheads). In (B) and (C) the asymmetric synapses (T) upon the soma (S) at arrows in (A) are shown at higher magnification. F, symmetric synapse upon the dendrite. A, bar = 1 μm; B, and C, bar = 0.5 μm.

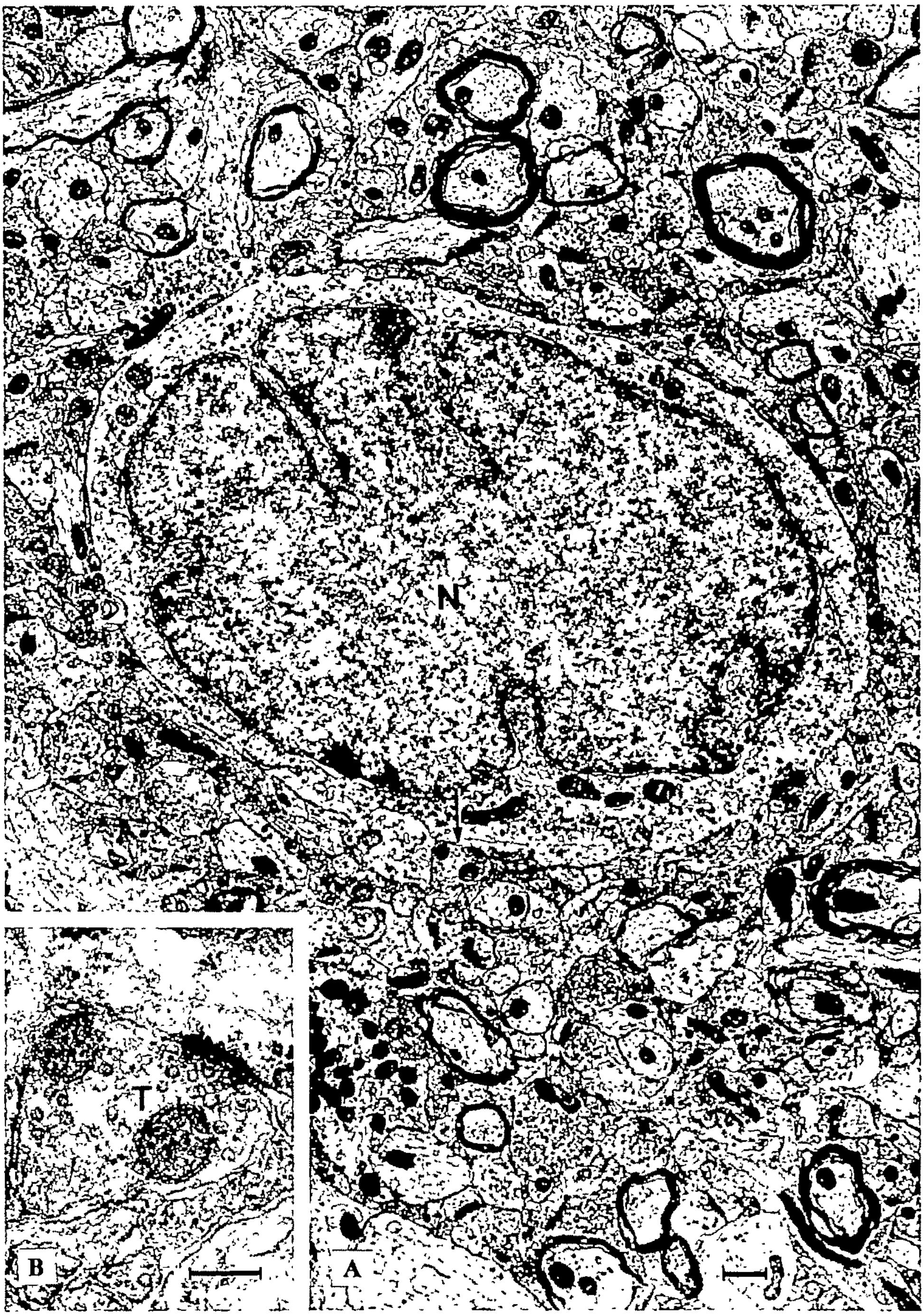

FIG. 3. A small stellate neuron (N) from layer II of the motor cortex of the cat (A) with an asymmetric synaptic contact upon its soma (arrow) shown at higher magnification (T) in (B). A, bar = 0.75 μm; B, bar = 0.02 μm.

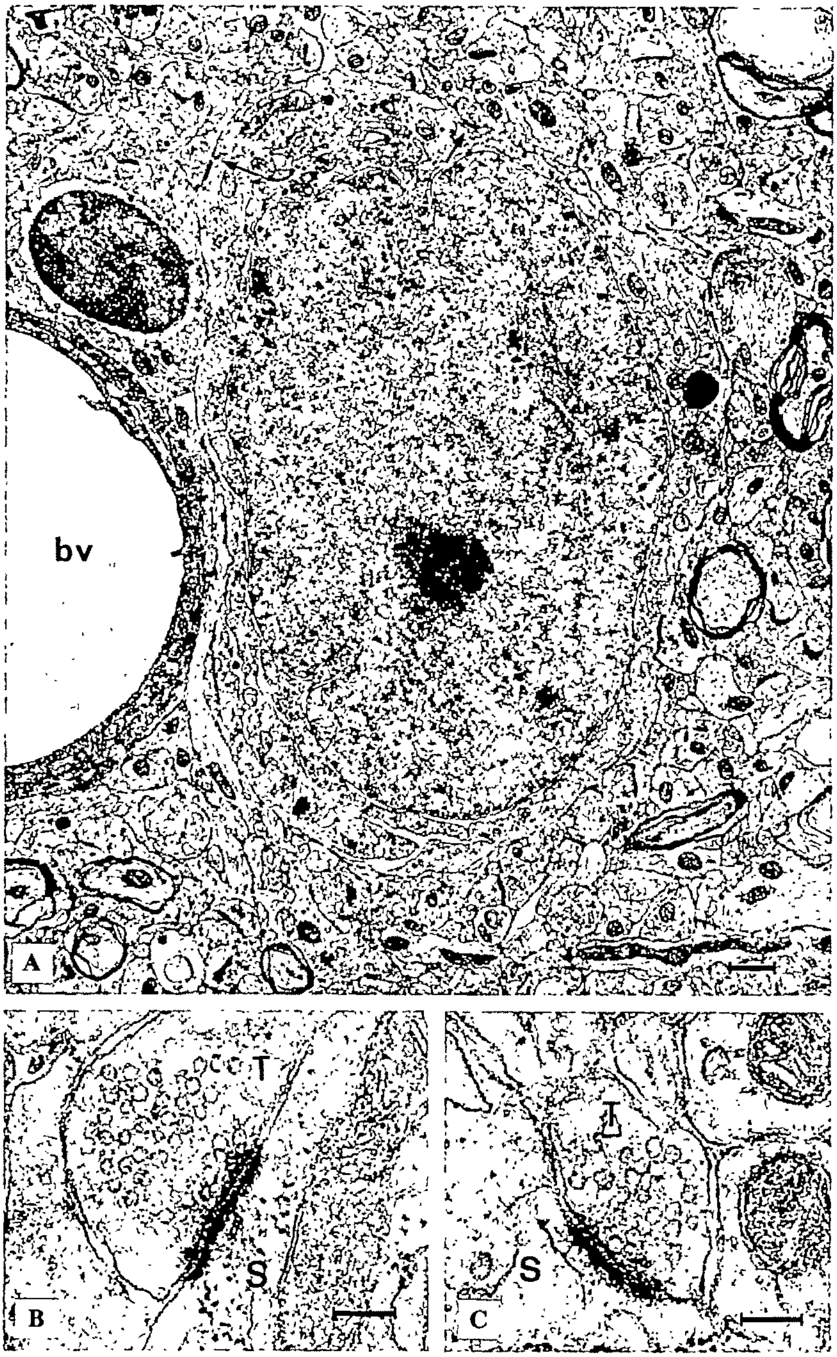

FIG. 4. An example of a fusiform cell from layer IV of the visual cortex of the cat (A) with an adjacent blood vessel (bv). The long axis of the fusiform cell is arranged perpendicular to the pial surface. Asymmetric synapses (arrows) upon the soma (S) are shown at higher magnifications (T) in B and C. A, bar = 0.75 μm; B and C, bar = 0.02 μm.

(25 per cent) is less than in the visual cortex. In the monkey the pyramidal cells of the motor cortex have approximately 25 per cent more synapses than the visual cortex but differences between the areas in the cat and rat are not significant. The number of synapses upon the small stellate cells in the different areas and species show changes parallel to those for the pyramids; the data for the synapses upon the large stellate cells have not been analysed statistically because the sample is small, but the figures are given in Table 2.

DISCUSSION

It should be emphasized that this study is based upon the electron microscopic appearance of only the cell bodies of the neurons of the neocortex, but with this qualification it is significant that using the same criteria for the identification of the cell type in the visual and motor areas of the rat and cat the proportion of the pyramidal and non-pyramidal cells has been found to be surprisingly similar in the two areas and in the corresponding areas of the monkey. This finding suggests that in mammalian evolution the proportions of the main types of cell in the neocortex, as well as the absolute number of cells through the depth, has remained the same (Rockel, Hiorns and Powell, 1980). No increase in the non-pyramidal or interneuron has occurred as has been generally thought, and the constant and large proportion of pyramidal cells reflects the numerous and widely distributed projections from the cortex. The proportions of these types of cells in the areas which have been investigated in different species are of the same order of magnitude, and the small differences between the figures in the present study and those presented by Tömböl (1974) are probably due largely to technical factors. In the visual cortex Tömböl obtained a lower proportion of pyramidal cells (59 per cent) and a correspondingly higher figure of small stellates (33 per cent). The different proportions found by Tömböl are probably due to her sample being restricted to somata with nucleoli only, as one would predict that the smallest cell, the small stellate, would then be relatively more frequent. This is confirmed by the fact that when the cells with nucleoli only in Sloper's sample (1973) were analysed the number of pyramidal cells decreases and the small stellates increase (Sloper *et al.*, 1979).

The cell body of the large non-pyramidal stellate neuron has several distinctive features of its cytoplasm and has many synapses, and the descriptions of it by different authors in a number of cortical areas in several species are consistent. It had not been realized, however, that the proportion of these cells is relatively small, being less than 10 per cent; as this figure is probably valid, since the cell is readily recognized and there is agreement as to its identity between different workers, it is significant that the proportion is so similar in the different areas and species. There is evidence that in the motor cortex (Gatter, Sloper and Powell, 1978; Sloper *et al.*, 1979) this large non-pyramidal or stellate cell of electron microscopic studies corresponds with the basket cell described in Golgi-impregnated material (Cajal, 1911; Marin-Padilla, 1969, 1970), and in the somatic sensory area the cell body

TABLE 1. THE PROPORTION OF DIFFERENT CELL TYPES IN THE MOTOR AND VISUAL CORTICES OF THE CAT, RAT AND MONKEY

Animal		*Pyramidal*	*Non-pyramidal*		*Total sample*
			Large stellate	*Small stellate*	
Cat 526	Motor	64 (67%)	3 (3%)	29 (30%)	96
	Visual	66 (66%)	5 (5%)	30 (29%)	101
Cat 543	Motor	67 (67%)	5 (5%)	28 (28%)	100
	Visual	67 (67%)	5 (5%)	28 (28%)	100
Rat 1	Motor	73 (65%)	7 (6%)	32 (29%)	112
	Visual	85 (72%)	4 (3%)	29 (25%)	118
Rat 2	Motor	68 (64%)	8 (8%)	30 (28%)	106
	Visual	80 (69%)	9 (8%)	27 (23%)	116
Rat 3	Motor	67 (67%)	6 (6%)	27 (27%)	100
	Visual	62 (62%)	5 (5%)	33 (33%)	100
Monkey 126	Visual	62 (62%)	5 (5%)	33 (33%)	100

TABLE 2. THE MEAN NUMBERS OF SYNAPSES UPON THE SOMATA OF CELLS

Species	*Mean number (SD)*	
	Visual	*Motor*
	Pyramid	
Primate	1.43 ± 0.64	1.79 ± 0.97
Cat	2.49 ± 1.77	2.49 ± 0.82
Rat	2.52 ± 1.67	2.40 ± 1.42
	Small stellate	
Primate	1.22 ± 0.40	2.18 ± 1.34
Cat	2.38 ± 1.15	2.66 ± 1.55
Rat	2.08 ± 1.22	2.61 ± 1.34
	Large stellate	
Primate	9.2	8.4
Cat	7.5	4.5
Rat	8.8	6.8

of the Golgi-impregnated neuron identical to the basket cell is considerably larger than the other non-pyramidal cells (Jones, 1975). In immunocytochemical (Ribak, 1978) and combined Golgi-electron microscopic investigations (Peters and Fairén, 1978) of the rat visual cortex the large non-pyramidal neuron of electron microscopy has been identified as the aspinous or sparsely spinous stellate cell of Golgi material.

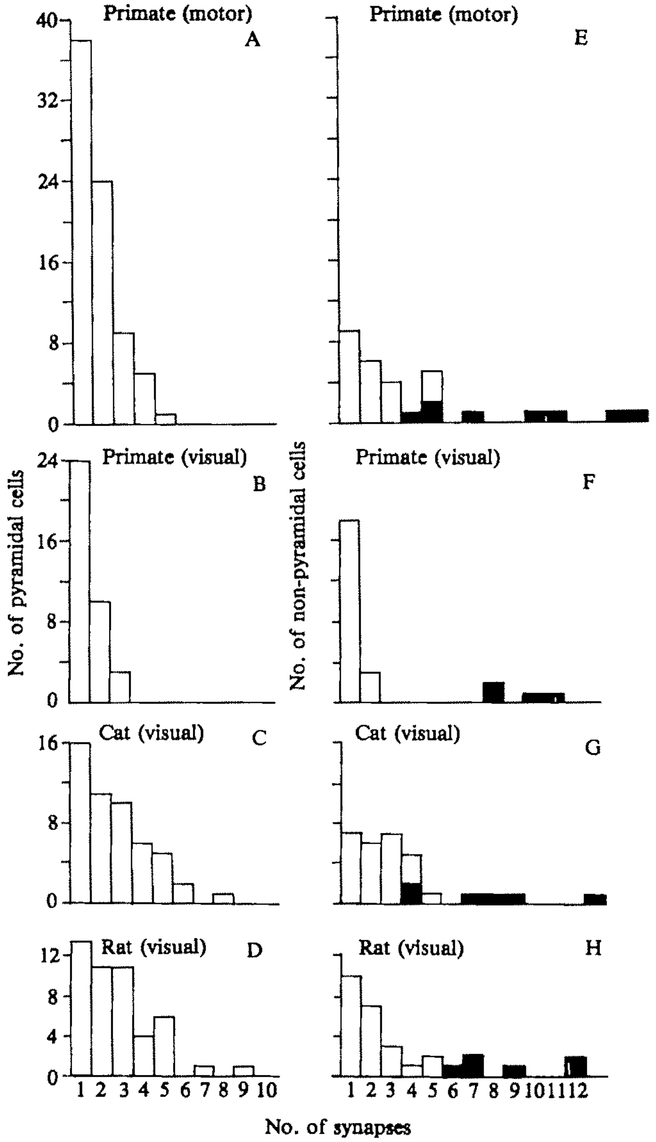

FIG. 5. Histograms showing the distributions of synapses upon the somata of pyramidal cells (A, B, C and D) and non-pyramidal cells (E, F, G and H) in the cortex of the rat, cat and primate. (Data for primate motor cortex from Sloper *et al.*, 1979). ■ large stellate cells.

In studies of the neocortex with the Golgi method several varieties of non-pyramidal neurons have been described and the identification of a second (the small stellate) and possibly a third (the fusiform) non-pyramidal neuron with the electron microscope is but an early stage in the attempt to recognize these types of neurons. In his account of the non-pyramidal or stellate cells of the parietal cortex of the rat Peters (1971) did not divide them into two distinct types, but on the basis of their size he described clearly small and large varieties. His description and illustration of the small cell are so similar to ours that it can be accepted that he recognized the same type of neuron, and he also found them to be often in groups of three or four. The granule cells of layer IV of the auditory cortex of the squirrel monkey (Smith and Moskowitz, 1979) also resemble the small stellates described here, and again they occur in groups with frequent membrane appositions between adjoining cells. More extensive electron microscopic studies of neuronal somata and their dendrites will lead to further sub-divisions of the small cells, especially in conjunction with methods for labelling cells so that they can be first identified with the light microscope. In their combined Golgi and electron microscopic study of the stellate cells in the visual cortex of the rat Peters and Fairén (1978) describe one cell (number 4) which was seen with the light microscope to be smaller than the others and had a different axonal arborization pattern. With the electron microscope the soma of this cell was also different and in all respects corresponded to our description of the small stellate in being smaller, having a nucleus with deep infoldings, little cytoplasm and few synapses of both types. On the basis of their appearance in Golgi material Feldman and Peters (1978) have classified the non-pyramidal neurons of the rat visual cortex into two main groups, the multipolar and fusiform, and it is possible that the fusiform type of soma found here and by Sloper (1973) and Tömböl (1974) is that of the second group of cells. From an electron microscopical examination of Golgi-impregnated spiny stellate cells in the visual cortex of the cat and monkey, it has been suggested that this class of cell lacks asymmetric synapses on to the soma (Le Vay, 1973). If this observation is confirmed, cells identified as pyramidal cells partly because of the absence of asymmetric synapses on the somata in the present and previous studies must include a proportion of spiny stellate cells.

Although the three types of neurons occur in the same proportions in the visual and motor cortex of the rat, cat and primate, the distribution of synapses upon their cell somata show certain differences which may affect the pyramidal and small stellate neurons and may occur either between different areas in the same animal or between the same functional area in different animals. The differences found for one cell type are paralleled by similar ones in the other. It is perhaps not surprising to find differences in the number of synapses between the monkey as compared with the cat and rat, and between the visual and motor areas in the monkey, but virtually identical figures for the two areas in both the cat and rat is unexpected. In the monkey there are fewer synapses upon the cells in the visual cortex than in the motor, and in both areas the figures are smaller than in the cat and rat.

The difference between the visual and motor areas of the monkey might be thought to be correlated with the difference in size of the cells between the two areas; this is probably not the sole explanation, however, because of the greater number of synapses upon the pyramids in the cat and rat where the cells are also smaller than those in area 4 of the monkey, and because the small stellate cells in the visual cortex of all animals are similar to each other in size and to those in the motor cortex of the monkey (Sloper *et al.*, 1979). The functional significance of the differences in number of synapses is uncertain without data for the number and distribution upon other parts of the neuron.

In view of the similar proportions of cells in the motor and sensory areas of different species, it would be of interest to determine whether the same is true in the 'association' areas of the frontal and parietal lobes. As the absolute number of neurons in a narrow strip through the depth of the cortex has been found to be the same in these association areas as in the motor and sensory areas of a number of species (Rockel *et al.*, 1980) it might be predicted that the proportions of cells would be the same in any functional area of the neocortex of any mammal; preliminary studies of the human temporal cortex suggest that this may be so.

SUMMARY

The neuronal cell somata in the cortex of the motor and visual areas of the cat and rat have been studied with the electron microscope. It has been possible to recognize the cell types which have been identified in the corresponding functional areas of the cortex of the monkey: pyramidal, large and small non-pyramidal. The large non-pyramidal or stellate cell has abundant endoplasmic reticulum and mitochondria and receives numerous asymmetric and symmetric synapses; the small non-pyramidal or stellate has a small amount of cytoplasm and few synapses of both asymmetric and symmetric nature. The proportions of these types of neurons are of the same order of magnitude in the different functional areas and in the different species: approximately two-thirds are pyramidal, slightly less than one-third are small stellate, and less than 10 per cent are large stellate. There is the same mean number of synapses upon the pyramidal and small stellate cell in the visual and motor areas of the rat and cat, but this number is less in the monkey being 50 per cent less in the visual cortex and 25 per cent less in the motor area.

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THE CLINICAL FEATURES OF HEREDITARY MOTOR AND SENSORY NEUROPATHY TYPES I AND II

by A. E. HARDING *and* P. K. THOMAS

(*From the Department of Neurological Science, Royal Free Hospital School of Medicine and the University Department of Clinical Neurology, Institute of Neurology, Queen Square, London*)

INTRODUCTION

THE first clear descriptions of peroneal muscular atrophy were made simultaneously by Charcot and Marie (1886) and Tooth (1886) although earlier accounts of similar cases had appeared. A disorder was defined, commonly with an onset in childhood, consisting of a denervating process that gave rise to slowly progressive weakness and muscle atrophy, first affecting the feet and legs and much later the hands and forearms. The early involvement of the peroneal muscles, the occurrence of foot deformity and the lesser severity of sensory loss were emphasized, as was the tendency of the disorder to affect more than one member of a family. The pathology was debated, Charcot and Marie favouring a myelopathy, Tooth a peripheral nerve disturbance. Thereafter, until the studies performed over the past decade or so, the situation became progressively more confused.

The first source of confusion was the recognition of hypertrophic neuropathy by Gombault and Mallet (1889) in a patient thought to be suffering from tabes dorsalis. In 1893, Dejerine and Sottas identified these changes in a brother and sister, born to apparently unaffected parents, with a severe progressive sensorimotor neuropathy and thickened peripheral nerves. The concept of hypertrophic neuropathy or Dejerine-Sottas disease thus arose (Dejerine, 1896) despite early doubts that the condition was not clearly separable from Charcot-Marie-Tooth disease (Marinesco, 1894). Hoffmann (1912) actually delineated cases with the clinical features of peroneal muscular atrophy but which he separated because of the presence of thickened nerves. These were sometimes designated as Hoffmann's disease. Roussy and Cornil (1919) later defined cases of adult onset without a family history but in which the histological changes in the nerves were similar, and Nattrass (1921) described cases that pursued a relapsing course. The concept of a unitary entity, Dejerine-Sottas disease, was finally discarded when it was shown that the concentric cell proliferation that characterizes hypertrophic neuropathy is the non-specific consequence of recurrent segmental demyelination and remyelination which is observed in a wide variety of inherited and acquired disorders (Thomas and Lascelles, 1967).

A second source of confusion was the concept of the Roussy-Lévy syndrome (1926). These two authors described cases of childhood onset with pes cavus and tendon areflexia, distal weakness in the limbs, tremor in the upper limbs, ataxia of gait, and distal sensory loss. Even from the outset, the separate identity of this syndrome was questioned. Rombold and Riley (1926) considered that it was a *forme fruste* of Friedreich's ataxia whereas Symonds and Shaw (1926) emphasized its similarity to peroneal muscular atrophy. Spillane (1940) argued that it was a separate entity, but described cases resembling the Roussy-Lévy syndrome, Friedreich's ataxia and peroneal muscular atrophy in the same family. In a follow-up study of the original family reported by Roussy and Lévy, Lapresle (1956) stated that the cases tended to evolve into a position intermediate between Friedreich's ataxia and peroneal muscular atrophy. He and Salisachs (1973) later found hypertrophic changes in a nerve biopsy from a member of the Roussy-Lévy family.

The first semblance of order in the classification of peroneal muscular atrophy and related disorders became possible with the introduction of nerve conduction studies in the mid-nineteen-fifties. Henriksen (1956) and Gilliatt and Thomas (1957) found severe slowing of motor nerve conduction velocity in some patients with peroneal muscular atrophy; other cases did not show this. Dyck and Lambert (1968*a*, *b*) found that this was consistent within families and correlated the conduction changes with nerve biopsy findings. They defined two broad groups. The first comprised cases with severely reduced conduction velocity associated morphologically with segmental demyelination, sometimes accompanied by hypertrophic changes. This group was subdivided into the hypertrophic neuropathies of Charcot-Marie-Tooth and Dejerine-Sottas types. The second group comprised neuronal degenerations with relatively preserved nerve conduction velocity and little evidence of segmental demyelination. It was subdivided into the neuronal form of Charcot-Marie-Tooth disease, progressive spinal muscular atrophy of Charcot-Marie-Tooth type, and hereditary spastic paraplegia and spinocerebellar degeneration with peroneal muscular atrophy. This broad subdivision was confirmed by Thomas and Calne (1974) and Thomas, Calne and Stewart (1974). For simplicity, the 'hypertrophic' and 'neuronal' forms of peroneal muscular atrophy have come to be termed hereditary motor and sensory neuropathy (HMSN) types I and II (Thomas *et al.*, 1974; Dyck, 1975). It was concluded that the Roussy-Lévy syndrome represented a clinical variant of type I HMSN and did not constitute a genetic entity (Dyck and Lambert, 1968*a*; Lascelles, Baker and Thomas, 1970; Thomas *et al.*, 1974). The cases described by Hoffmann (1912) are obviously examples of type I HMSN.

Although Buchthal and Behse (1977) later also supported this subdivision, it has not been universally accepted. Thus Humberstone (1972) and Salisachs (1974) found a random distribution of conduction velocities in peroneal muscular atrophy and Brust, Lovelace and Devi (1978) and Davis, Bradley and Madrid (1978) defined groups with intermediate conduction velocities. A further analysis of a larger group of cases has therefore been undertaken and an attempt made to quantitate both their classification and the differences in the clinical features between the separate categories.

CASE MATERIAL AND METHODS

The series comprises all patients with peroneal muscular atrophy referred to one of us (PKT) since 1966, and includes those already reported by Thomas and Calne (1974) and Thomas *et al.* (1974). Cases were only accepted which were diagnosed as uncomplicated peroneal muscular atrophy on clinical grounds and thus more complex syndromes such as familial spastic paraplegia with amyotrophy were excluded. Each patient was examined clinically by one of us and electrophysiological studies performed. Denervation was confirmed by electromyographic sampling with a concentric needle electrode in affected muscles. Motor nerve conduction velocity in the median and peroneal nerves was estimated, usually with surface recording electrodes over abductor pollicis brevis and extensor digitorum brevis, respectively, or with a needle electrode in severely denervated muscles. The extensor digitorum brevis was often found to be totally denervated. Sensory conduction was examined in the median and ulnar nerves with percutaneous stimulation and recording. In the lower limbs, the peroneal ascending mixed nerve action potential was examined in the earlier cases and the sural sensory nerve action potential in later cases employing percutaneous stimulation and needle electrode recording. Near relatives were similarly examined whenever possible. For children, a more restricted examination was sometimes necessary.

A total of 262 affected individuals was collected. Included in this series were 34 cases with the clinical syndrome of peroneal muscular atrophy without sensory loss, which displayed electromyographic evidence of denervation in the distal musculature, normal or slightly reduced motor nerve conduction velocities and normal sensory action potentials. They have been classified as examples of distal spinal muscular atrophy and have been described elsewhere (Harding and Thomas, 1980*a*). The remaining 228 patients represent examples of hereditary motor and sensory neuropathy and constitute the largest series so far collected.

Observations on the clinical and electrophysiological findings were recorded quantitatively and stored in a Hewlett Packard 2100 computer (RTE II operating system). Using the techniques of cluster analysis, no more satisfactory way of subdividing the data other than in terms of the nerve conduction findings emerged (Harding, Thomas Wadbrook and Douglas, 1978). Statistical analysis of the data was performed using Yates χ^2 test (Yates, 1934) unless otherwise indicated.

RESULTS

Genetic Classification

The series of 228 patients comprises 120 index cases and 108 affected relatives diagnosed during the course of the study. Nerve conduction studies were performed in 180 patients. A value for motor conduction velocity for the median nerve was obtained in 170 and for the peroneal nerve in 84. In 72 cases a value could not be obtained for the latter nerve as the extensor digitorum brevis muscle was totally denervated. Fig. 1 shows the distribution of motor conduction velocity for the median and peroneal nerves. Velocities range continuously from normal to very low values in both nerves. The distributions are bimodal, with a larger group with severely reduced conduction velocities and a smaller group with normal or moderately reduced velocities.

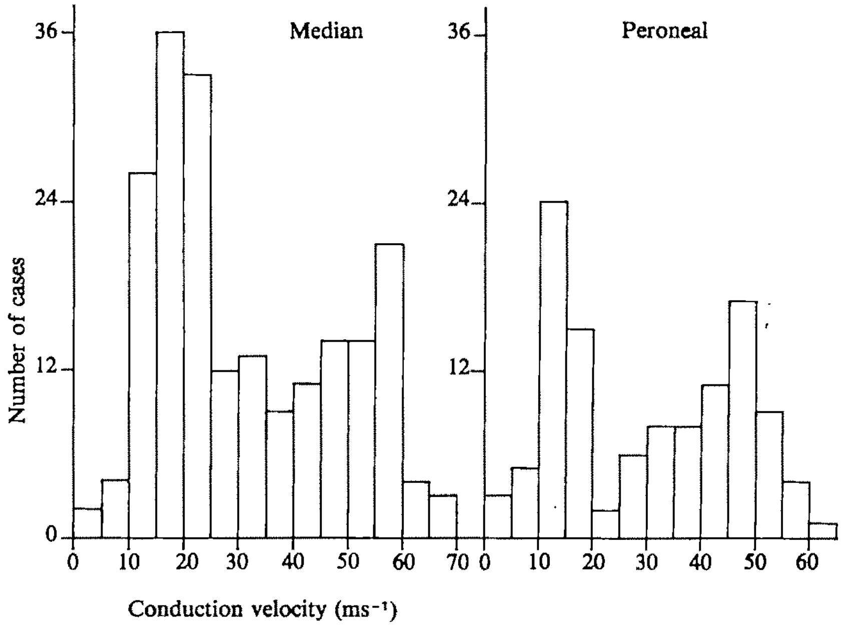

FIG. 1. Frequency distribution of motor conduction velocity in median and peroneal nerves in cases of hereditary motor and sensory neuropathy.

Fig. 2 shows the values for median motor conduction velocity in the index cases plotted against that of their relatives. A regression line has been calculated for the total data. This yields a highly significant correlation ($r = 0.79$; $P < 0.001$), indicating genetic heterogeneity in terms of motor conduction velocity. The values clearly form two clusters, corresponding to the two peaks in the histogram of fig. 1. The separation occurs at approximately 38 m s^{-1}. The cases were therefore divided by lines crossing both axes at this value. With this cut-off level, only three individuals are misclassified: that is, when families are allocated to one or other category depending upon motor conduction velocity in the index case, in three instances relatives have velocities that fall just outside the appropriate cluster.

Individuals with a median motor conduction velocity greater than 38 m s^{-1} correspond to HMSN type II. Although there is a positive regression line for these cases, this is not statistically significant ($r = 0.41$; $P > 0.05$), indicating that no further subdivision is possible in terms of motor conduction velocity. For those individuals with a median motor conduction velocity below 38 m s^{-1}, there is a statistically significant positive regression ($r = 0.71$; $P < 0.001$) indicating additional genetic heterogeneity. Within this group are four families (8 individuals) demonstrating probable autosomal recessive inheritance. Their mean median motor conduction velocity is 16.5 ± 6.2 m s^{-1}, which is significantly less than that for the dominant cases (21.7 ± 7.0 m s^{-1}; $P < 0.05$). On removing these cases from the plotted data, the value for r becomes 0.67. This is still significant, but less so than for the total cases in this group. Thus the genetic heterogeneity may be partly but not wholly explained by the presence of the autosomal recessive cases. There is no obvious way of further subdividing these cases and they have therefore been designated for the remaining analyses as HMSN type I.

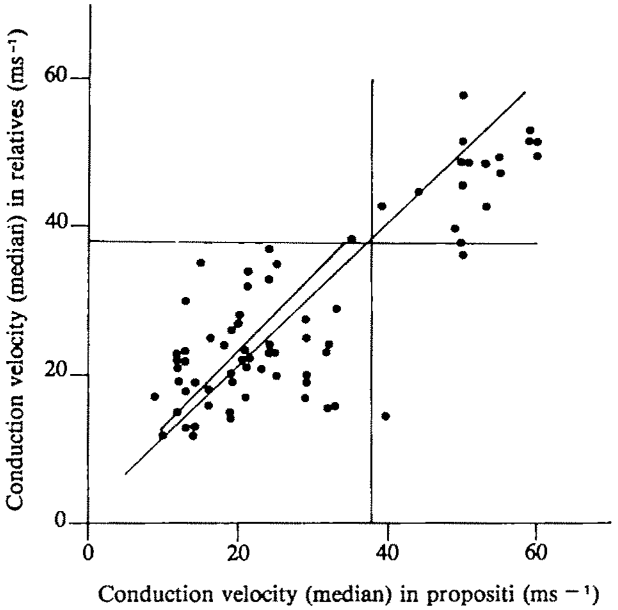

FIG. 2. Relationship between motor conduction velocity in median nerve for propositi and relatives in patients with hereditary motor and sensory neuropathy.

This classification gives a total of 139 cases of HMSN type I and 39 cases of type II. Examination of relatives revealed affected members in 42 type I families and 12 type II families. Electrophysiological abnormalities were not detected in individuals who showed no clinical abnormality. A further 8 type I and 7 type II index cases had a positive family history of foot deformity and/or weakness in the lower or upper limbs. Unfortunately, their relatives were either unco-operative or unavailable for further study.

For both types I and II HMSN, the inheritance in the majority was clearly of autosomal dominant pattern: 38 type I families and 11 type II. As already noted, there were 4 type I families with probable autosomal recessive inheritance. All these contained two affected siblings. The parents of three pairs of these siblings were examined and found to be clinically and electrophysiologically normal. In one family, the parents were first cousins.

The type II cases contained 2 probable autosomal recessive families, again with two affected siblings in each family. In both, the parents were first cousins. One pair was examined and was normal both clinically and electrophysiologically. These families demonstrating autosomal recessive inheritance will be described in greater detail elsewhere (Harding and Thomas, 1980*b*).

Forty-two patients presented with the clinical features of peroneal muscular atrophy but had no relevant family history. It was possible to examine the parents and sibs in 10 instances. All were clinically and electrophysiologically normal. The index cases have been classified as sporadic: 26 fall into the type I category and 16 into type II. For the purposes of analysis, the probable recessive cases and the sporadic cases have been grouped together. The latter could be examples of recessive inheritance, new dominant mutations or phenocopies. Further discussion of this question, together with segregation analyses, will be presented separately (Harding and Thomas, 1980*c*).

This classification is summarized in Table 1.

TABLE 1. CLASSIFICATION OF HEREDITARY MOTOR AND SENSORY NEUROPATHY

		No. of cases	
Type I			
Dominant		139	(39 families)
Recessive		8	(4 families)
Sporadic		26	
	Total	173	
Type II			
Dominant		37	(11 families)
Recessive		3	(2 families)
Sporadic		15	
	Total	55	

Clinical Features

The clinical features of these patients are compared in fig. 3 and Tables 2 to 6. The age of onset (fig. 3) differs in the two types of HMSN. The majority of type I cases developed symptoms during the first decade; most of the remainder became symptomatic in the second decade and very few after that. The peak age of onset in the type II patients was in the second decade with a substantial number not developing symptoms until much later, sometimes not until the seventh decade. In the type I families, 19 relatives of index cases were asymptomatic but clinically affected; 8 affected relatives of type II cases had no symptoms.

Distal weakness in the upper limbs occurred in two-thirds of type I cases, but only half of type II cases (Table 2). Lower limb weakness, either moderate or severe, had a similar frequency in both groups. However, the sporadic/recessive type I cases were more commonly found to have severe weakness in the lower limbs than those with autosomal dominant inheritance.

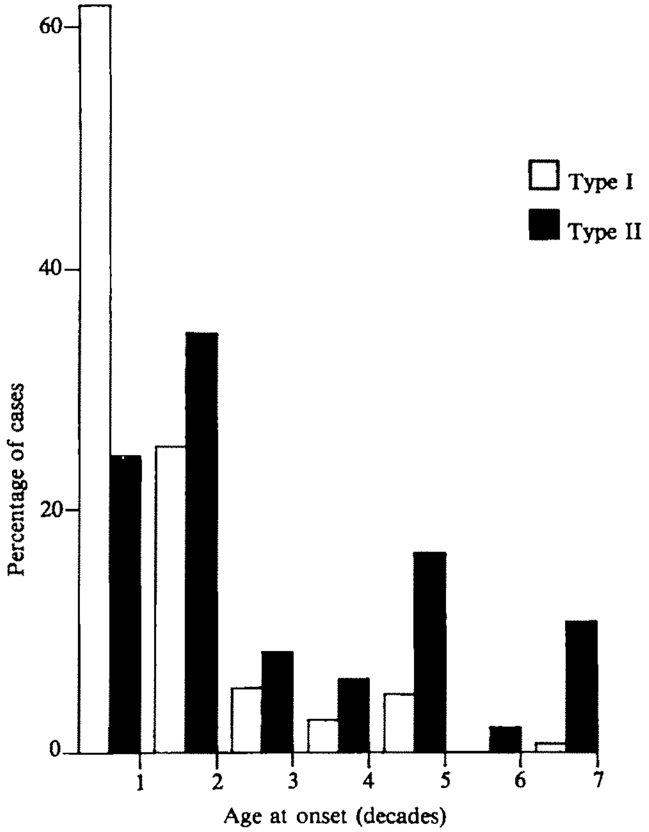

FIG. 3. Histogram showing distribution of age of onset (in decades) in type I and II hereditary motor and sensory neuropathy.

Tremor and ataxia were assessed together, as distinguishing these features separately is often difficult in practice. They were more common in the upper limbs in type I patients, but occurred to a similar extent in both types of HMSN in the lower limbs (Table 3).

TABLE 2. HEREDITARY MOTOR AND SENSORY NEUROPATHY: INCIDENCE OF WEAKNESS

	No. of cases			
	Type I		*Type II*	
Upper limbs				
Total	116 (67)		28 (51)	$P < 0.05$
Dominant	89 (64)	n.s.	18 (49)	n.s.
Sporadic/recessive	27 (79)		10 (55)	
Lower limbs				
Total	150 (87)		52 (94)	n.s.
Dominant	118 (85)	n.s.	34 (92)	n.s.
Sporadic/recessive	32 (94)		18 (100)	
Severe lower limb weakness				
Total	59 (34)		18 (33)	n.s.
Dominant	40 (29)	$P < 0.01$	12 (32)	n.s.
Sporadic/recessive	19 (56)		6 (33)	

Percentage figures in brackets.

Reflex changes were more marked in type I HMSN (Table 4). Total tendon areflexia occurred in only 9 per cent of type II cases, but in 58 per cent of type I patients. Loss of the knee jerks followed a similar pattern. In both types of HMSN the ankle jerks were lost in the majority of cases. Extensor plantar responses occurred in 3 patients in the type I group; in the vast majority, however, for both types, the responses were flexor or absent.

Sensory loss (Table 5) was more obtrusive in type I than type II cases. Vibration sense was the most severely affected modality in both groups and joint position sense the best preserved.

TABLE 3. HEREDITARY MOTOR AND SENSORY NEUROPATHY: INCIDENCE OF TREMOR/ATAXIA

	No. of cases		
	Type I	*Type II*	
Upper limbs	67 (39)	9 (16)	$P < 0.01$
Lower limbs	40 (23)	10 (18)	n.s.

Percentages in brackets. Difference between dominant and sporadic/recessive groups not significant.

TABLE 4. HEREDITARY MOTOR AND SENSORY NEUROPATHY: INCIDENCE OF TENDON AREFLEXIA

	No. of cases		
	Type I	*Type II*	
Upper limbs	101 (58)	5 (9)	$P < 0.02$
Knee jerk	67 (70)	10 (18)	$P < 0.02$
Ankle jerk	154 (89)	44 (80)	n.s.

Percentages in brackets. Differences between dominant and sporadic/recessive groups not significant.

Table 6 compares the incidence of some further clinical features. Foot deformity was frequent in both groups, although again more common in type I cases. It was also more frequent in the dominant form of type II HMSN as compared with the sporadic/recessive patients. Scoliosis was present in more type I than type II cases: it was more frequent in the type I sporadic/recessive group. Nerve thickening was predictably exclusive to the type I group.

Additional features occurred in very few patients, probably mainly because of the criteria adopted for inclusion of the index cases in the study. Four (all type I) had unequal pupils; these were of Argyll Robertson type in one. Four (one type I, three type II) had mild to moderate sensorineural deafness; one of these (type II) also had optic atrophy. Three (one type I, two type II) had mild dysarthria. Ten cases of HMSN type I had finger contractures in association with severe weakness of the small hand muscles. Six patients had required amputations of varying extent as a result of severe deformity or ulceration related to dense sensory loss; five of these were type I HMSN. Recurrent dislocation of the patellæ occurred as a presenting symptom in 2 families with autosomal dominant type I HMSN.

TABLE 5. HEREDITARY MOTOR AND SENSORY NEUROPATHY: INCIDENCE OF SENSORY LOSS

	No. of cases		
	Type I	*Type II*	
Light touch	89 (53)	20 (36)	$P < 0.05$
Pain	89 (53)	17 (31)	$P < 0.05$
Joint position sense	78 (46)	14 (25)	$P < 0.01$
Vibration sense	117 (69)	31 (56)	n.s.

Percentages in brackets. Differences between dominant and sporadic/recessive groups not significant.

TABLE 6. HEREDITARY MOTOR AND SENSORY NEUROPATHY: INCIDENCE OF SKELETAL DEFORMITY AND NERVE THICKENING

	No. of cases			
	Type I		*Type II*	
Pes cavus				
Total	125 (72)		28 (51)	$P < 0.01$
Dominant	100 (72)	n.s.	24 (65)	$P < 0.05$
Sporadic/recessive	25 (73)		4 (22)	
Scoliosis				
Total	24 (14)		2 (3.6)	$P \hat{=} 0.05$
Dominant	14 (10)	$P < 0.01$	1 (2.7)	n.s.
Sporadic/recessive	10 (29)		1 (5.5)	
Nerve thickening				
Total	49 (28)		0	$P < 0.02$
Dominant	40 (29)	n.s.	0	
Sporadic/recessive	9 (26)		0	

Percentages in brackets.

TABLE 7. HEREDITARY MOTOR AND SENSORY NEUROPATHY: ELECTROPHYSIOLOGICAL FINDINGS

	Mean motor nerve conduction velocity ($m\ s^{-1}$)		
	Type I	*Type II*	*Control**
Median	21.1 ± 7.0 {$P < 0.001$}	51.9 ± 9.0 {$P < 0.01$}	57.2 ± 4.2
Peroneal	16.6 ± 7.7 {$P < 0.001$}	44.2 ± 10.1 {$P < 0.05$}	49.7 ± 7.1
	Recessive	*Dominant*	*Sporadic*
Median			
Type I	16.5 ± 6.2 {$P < 0.05$}	21.7 ± 7.0 {n.s.}	18.4 ± 7.4
Type II		48.5 ± 6.6 {n.s.}	52.4 ± 8.3

	Median sensory nerve action potentials *No. of cases*		
	Type I	*Type II*	
Absent	115 (93)	37 (73)	$P < 0.02$**
Reduced	9 (7)	14 (27)	

Percentage values in brackets. Statistical comparisons by Student's t test. Differences in peroneal motor conduction velocity between dominant and sporadic/recessive groups not significant. * From Thomas *et al.* (1959). ** By χ^2.

The electrophysiological results are summarized in Table 7. Mean median motor conduction velocity was 21.1 ± 7.0 and 51.9 ± 9.0 m s^{-1} in the total type I and type II HMSN patients, respectively. Both of these values differ significantly from controls (Thomas, Sears and Gilliatt, 1959). As has been noted above, the mean motor conduction velocity for type I patients with probable autosomal recessive inheritance is significantly less than for the dominantly inherited group. The mean motor conduction velocity for the sporadic cases is not statistically significantly different from either the recessive or the dominant groups. The values for motor conduction velocity in the sporadic/recessive and dominant cases in type II HMSN are not significantly different.

The values for the mean peroneal motor conduction velocity (16.6 ± 7.7 m s^{-1} for type I and 44.2 ± 10.1 m s^{-1} for type II) again differ considerably from control values. A separate value could not be calculated for type I patients with autosomal recessive inheritance as the extensor digitorum brevis was completely denervated in 6 out of the 8 patients. The mean values for the sporadic/recessive and dominant cases are not significantly different for either type of HMSN.

The median sensory nerve action potential was more frequently completely absent in type I patients (93 per cent) than in type II; in the latter, 27 per cent had a potential of reduced amplitude.

Objective assessment of severity in these cases was difficult. As muscle weakness was usually the most significant feature leading to disability, a 'weakness score' was devised as an indication of severity. Weakness was assessed on a scale of 0–2 in the lower and upper limbs and the score for each combined. This gives a possible 'mean weakness score' ranging from 0–4 in each case. The mean weakness scores for each group are shown in Table 8. There is no overall significant difference

TABLE 8. HEREDITARY MOTOR AND SENSORY NEUROPATHY: MEAN WEAKNESS SCORES

	Type I		*Type II*	
Total	1.99 ± 1.1		1.89 ± 1.0	n.s.
Dominant	1.88 ± 0.88	$P < 0.02$	1.84 ± 1.1	n.s.
Sporadic/recessive	2.44 ± 0.93		1.99 ± 0.93	

	Male	*Female*	
Type I			
Total	2.13 ± 1.22	1.59 ± 1.01	$P < 0.02$
Dominant	2.02 ± 1.3	1.46 ± 1.4	$P < 0.01$
Sporadic/recessive	2.5 ± 1.0	2.33 ± 0.78	n.s.
Type II			
Total	2.24 ± 0.93	1.5 ± 0.97	$P < 0.01$
Dominant	2.44 ± 0.96	1.38 ± 0.97	$P < 0.001$
Sporadic/recessive	2.0 ± 0.86	2.0 ± 1.0	n.s.

Statistical comparisons by t test.

between types I and II. The score for the type I sporadic/recessive group, however, is significantly higher than that for the other groups. Mean weakness scores were calculated separately for males and females (Table 8). Males were more severely affected than females, the most significant difference being in the autosomal dominant cases of both type I and type II HMSN. Asymptomatic but clinically affected family members were more commonly female than male (18 out of 27).

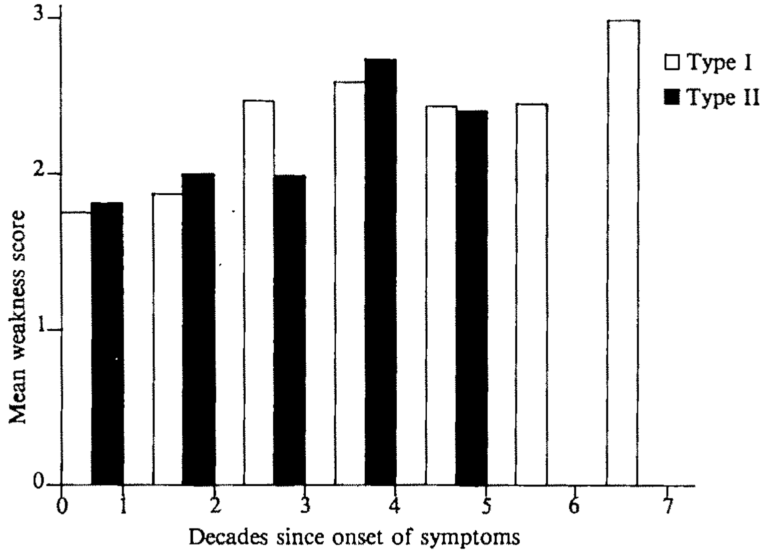

FIG. 4. Relationship between mean weakness score and duration of symptoms (in decades) in type I and II hereditary motor and sensory neuropathy.

Fig. 4 shows the weakness score in both types of HMSN plotted against the number of decades since the onset of symptoms. Both groups show a progressive increase in the weakness score with time. There is a statistically significant positive correlation ($r = 0.87$; $P \simeq 0.01$) between the severity of weakness and duration of the disease after the onset of symptoms in the type I group, but in the type II patients this is not so ($r = 0.34$; $P > 0.05$).

DISCUSSION

Genetic Classification of HMSN

This study has confirmed the finding of Dyck and Lambert (1968*a*, *b*) and Thomas and Calne (1974) that HMSN is divisible in terms of median motor conduction velocity into at least two main groups. The median rather than the peroneal nerve was chosen, as in the previous study (Thomas and Calne, 1974), since abductor pollicis brevis was less frequently totally denervated. Moreover, in a severely denervated muscle with only a few surviving motor axons, the danger exists of obtaining a spuriously low value for motor conduction velocity. The two groups in the present series, HMSN types I and II, consist respectively of patients with a median motor conduction velocity either below or above 38 m s^{-1}. They correspond to the hypertrophic neuropathy of Charcot-Marie-Tooth type and the neuronal form of Charcot-Marie-Tooth disease described by Dyck and Lambert (1968*a*, *b*). Their approximate dividing value for median motor conduction velocity was 40 m s^{-1}, although minor degrees of overlap were noted. The cases of Brust *et al.* (1978) were categorized, using upper limb motor conduction velocities, almost identically. Buchthal and Behse (1977) have similarly divided patients with peroneal muscular atrophy into two categories, but on the basis of sensory conduction velocity in the sural nerve. This was found to be a more effective discriminant than motor conduction velocity. Their 'hypertrophic' type had sural nerve conduction velocities of less than 32 m s^{-1} and the 'neuronal' type velocities of over 37 m s^{-1}.

The classification adopted in the present paper is supported by virtually complete concordance within families for motor conduction velocities. By contrast, Myrianthopoulos, Lane, Silberbert and Vincent (1964), Salisachs (1974) and Brust *et al.* (1978) have described substantial discordance within families with respect to motor conduction velocities. The degree of variation is too great to be explicable in terms of recordings from severely denervated muscles. Such instances appear to be rare, but are potential flaws in the genetic classification of peroneal muscular atrophy using motor conduction velocity. There is probably some tendency for less severely affected individuals to display a less marked reduction in motor conduction velocity, but this effect is not large. The failure of motor conduction velocity to diminish with age both in type I and type II HMSN (Amick and Lemmi, 1963; Nielsen and Pilgaard, 1972; Thomas and Calne, 1974; Davis *et al.*, 1978) supports this view.

A major departure from this classification into two main types of peroneal muscular atrophy has been proposed by Bradley and colleagues (Bradley, Madrid and Davis, 1977; Davis *et al.*, 1978). Their cases were grouped into hypertrophic (< 25 m s^{-1}), intermediate (25–45 m s^{-1}) and neuronal types (> 45 m s^{-1}) on the basis of median motor conduction velocity. This grouping was supported by concordance of conduction velocity within the families, differences in severity between the three groups and the finding of 'intermediate' histological changes in the patients with a median conduction velocity of 25 to 45 m s^{-1}. It is impossible to define such an intermediate group on the basis of motor conduction velocity from the data presented here; as can be seen from fig. 2, there are several propositi with velocities in the 25 to 35 m s^{-1} range who had relatives with velocities below 25 m s^{-1} and *vice versa*.

It is of interest to note that nearly all the cases recorded by Davis *et al.* (1978) possess values for motor conduction velocity of less than 45 m s^{-1}, with only three cases (in 2 families) classified as the neuronal type of peroneal muscular atrophy. A considerable number of the patients described here have velocities higher than 45 m s^{-1} and in the study by Buchthal and Behse (1977), the neuronal type of peroneal muscular atrophy was more common than the hypertrophic form. This may be the result of regional differences in gene frequencies.

Although an intermediate group of patients defined by Bradley's criteria cannot be identified in the present series, there is statistical evidence that the type I cases are genetically heterogeneous in terms of motor conduction velocity. Furthermore, Thomas *et al.* (1974) have previously noted a suggestion of heterogeneity in type I cases from an analysis of the correlations in age of onset between siblings and between parents and offspring. This does not lead to any practical method for the further subdivision of this group, as there is considerable variation of age of onset, that is, the age at which symptoms develop, within individual families. Similarly there exist no means, other than the application of statistical techniques, for splitting the type I cases in terms of motor conduction velocity. For the present, therefore, further analysis of the clinical features necessarily has to be confined to the comparison of types I and II HMSN.

In both types of HMSN, the majority of cases exhibit autosomal dominant inheritance. There are cogent genetic reasons for analysing these separately from autosomal recessive or sporadic cases. Autosomal recessive inheritance is well documented in type I HMSN (Dyck and Lambert, 1968*a*), but to date there are no recorded instances of families with proven autosomal recessive type II HMSN. Certainly one of the type II families in this series, with two affected siblings and normal parents (both on clinical and electrophysiological grounds) is an example of the autosomal recessive form. The parents of these patients were first cousins, although the significance of this is diminished as the family was of Turkish Cypriot origin. These two siblings were also more severely affected than the majority of type II patients, with the older being almost chair-bound at the age of 17 years. In the second family, the cases were of later onset and exhibited a more benign course (Harding and Thomas, 1980*b*).

The status of Dejerine-Sottas disease or type III HMSN (Dyck, 1975) is confused. Dyck and Lambert (1968*a*) defined Dejerine-Sottas disease as a severe motor and sensory neuropathy presenting in infancy with abnormal motor development. In their examples the prognosis was worse than in the hypertrophic form of Charcot-Marie-Tooth disease and the cases were sporadic or of autosomal recessive inheritance. Motor conduction velocity was extremely low. Dyck, Lambert, Sanders and O'Brien (1971) produced evidence that the pathological changes included hypomyelination in addition to recurrent demyelination. Dyck, Ellefson, Lais, Smith, Taylor and Van Dyke (1970) also claimed that there was a generalized disturbance in the metabolism of ceramide hexosides and hexoside sulphates. This has not yet been confirmed by other laboratories. The stipulation of an onset in infancy for Dejerine-Sottas disease does not accord with the original description by the progenitors of this syndrome: in the family they reported, one sibling presented in infancy and the other was asymptomatic until the age of 14 years. The category of HMSN type III is probably best reserved for cases of severe infantile neuropathy with hypomyelination and markedly reduced nerve conduction velocity, including the congenital cases described by Lyon (1969), Kennedy, Sung and Berry (1977) and others. Most have been sporadic or of autosomal recessive inheritance. This is probably a genetically heterogeneous group. The present series contains no examples of this type. It is of interest that the homozygous expression of the dominant gene for type I HMSN gives rise to a clinical picture similar to that of type III HMSN (Kloepfer and Killian, 1974; Killian and Kloepfer, 1979).

In both type I and type II HMSN, the probable autosomal recessive cases have been grouped with the patients with no family history for comparison of the incidence of various clinical features. The reasons for this are twofold. First, the numbers of recessive cases are too small for them to be categorized separately for statistical analysis. Secondly, there is evidence that approximately half of the patients with no family history are examples of autosomal recessive inheritance (Harding and Thomas, 1980*c*). Unfortunately, there is no way of distinguishing these patients. None of the families described in this paper exhibited X-linked recessive inheritance.

Clinical Features of HMSN

The present observations clearly demonstrate that type I HMSN generally has an earlier age of onset than type II, with the latter developing symptoms at any time up to the seventh decade. Similar findings were obtained by Dyck and Lambert (1968*a*, *b*) and Buchthal and Behse (1977), although Brust *et al.* (1978) have described a wide range of ages of onset in both types. Thomas *et al.* (1974) employed the age of onset as a measure of the severity of the disorder. This is unsatisfactory in a number of ways as foot deformity is often present from early life, whereas symptoms of weakness are not noticed until later. In older patients, the age of onset of symptoms is frequently poorly remembered and close questioning of the patients often reveals a hint of disability before the admission of definite symptoms. In addition, cases in younger generations tend to be anticipated as the family is alerted to the possible appearance of abnormality. This was discussed by Penrose (1947/9) in relation to dystrophia myotonica. It is certainly true in the present series, where the mean age of onset of symptoms in parents was 23.7 years and in offspring 11.3 years. There were also an appreciable number of asymptomatic patients in both types of HMSN who had significant abnormalities on clinical and electrophysiological examination; obviously the onset of the disease cannot be dated in these cases.

In the present study, an assessment of muscle weakness has been undertaken; this is, generally speaking, an objective measure of the severity of the disease. It does depend to some extent on the duration of the disease although a statistically significant correlation was only demonstrable in the type I cases. Because of the correlation with age, Davis *et al.* (1978) attempted to apply an age-corrected weakness score. It is doubtful whether the nature of the data makes this a useful measure for the present purposes. Moreover, in comparisons between different groups comprising a large number of patients with a wide range and much variation in the duration of symptoms, the effect of applying a correction factor either for age or duration of symptoms is likely to be negligible. A disadvantage of the mean weakness score as a measure of disability is that a few of the patients studied were disabled more by ataxia than muscle weakness. Their numbers are small, with only two instances in the present series of patients with ataxia affecting all four limbs with minimal or absent weakness. Foot and spinal deformities are also an additional cause of disability.

It is of interest to note that the mean weakness score was similar in both dominant types of HMSN and the sporadic/recessive type II group. The type I sporadic/recessive group was more severely affected; this is in keeping with the general conclusion that the recessive form of a disorder is more severe than the dominant variety, and is supported by the finding of Killian and Kloepfer (1979) that the homozygous expression of the dominant type I HMSN gene produces a more severe clinical picture than the heterozygous state.

The incidence of tremor and ataxia is considerably higher in type I than type II HMSN. The features resemble the tremor that may be encountered in chronic relapsing idiopathic inflammatory neuropathy in which there is also widespread segmental demyelination in the peripheral nerves and often a severe reduction in nerve conduction velocity. Its features are also similar to those of essential tremor (Dyck and Lambert, 1968*a*; Salisachs, 1976). Cases exhibiting prominent tremor and ataxia would in the past have been designated as the Roussy-Lévy syndrome. It is now accepted that this is not a separate genetic entity, as such cases may be encountered within families in which other members display the usual features of peroneal muscular atrophy (Yudell, Dyck and Lambert, 1965; Lascelles *et al.*, 1970). In the present study, 14 patients with type I HMSN had significant ataxia or tremor in the absence of severe muscle weakness. Eight of these were members of families otherwise suffering from typical peroneal muscular atrophy. The remainder were sporadic cases. There was no correlation in this series between the presence of ataxia and tremor and scoliosis, a combination of features that has been suggested as typical of the Roussy-Lévy syndrome (Popow, 1932).

Tremor is not confined to the type I cases (Thomas *et al.*, 1974; Salisachs, Codina, Gimenez-Roldan and Zarranz, 1979). Two patients in this series with type II dominant HMSN had upper limb tremor and ataxia in the absence of muscle weakness or impaired joint position sense. Their relatives were clinically similar to other cases of type II HMSN. Total tendon areflexia is much more common in type I than in type II HMSN, as is true in general of demyelinating neuropathies. The clinical picture of the Roussy-Lévy syndrome with pes cavus, ataxia and tendon areflexia is thus likely to be encountered predominantly or perhaps solely in type I HMSN. An absolute distinction from Friedreich's ataxia is the finding of severely reduced nerve conduction velocity. No case of type II HMSN displaying the typical Roussy-Lévy syndrome was encountered in this series. Salisachs *et al.* (1979) have made similar observations.

Included in the dominant type I group of cases are 3 patients, from different families, with extensor plantar responses. The propositi and other relatives in these families all had either flexor or absent plantar responses. In view of this, it seems justifiable to categorize them as type I HMSN. The occasional presence of extensor plantar responses has been noted in other families with typical peroneal muscular atrophy (Davis *et al.*, 1978). A possible explanation is cord compression from hypertrophied spinal roots (Symonds and Blackwood, 1962). The assessment of the plantar responses in subjects with severely deformed feet may at times present difficulties.

The incidence of skeletal deformities is high in this series compared with others (Dyck and Lambert, 1968*a*; Brust *et al.*, 1978; Davis *et al.*, 1978). This is almost certainly due to selection bias. Many of the patients were derived from the neurological clinic at an orthopædic hospital and a large proportion of these presented with foot deformity; a small number were referred from a scoliosis clinic. The higher incidence of pes cavus and scoliosis in type I HMSN is in keeping with the earlier onset of this form. Again, the type I sporadic/recessive group have, in general, more severe foot deformity than the other patients. The occurrence of pes planus in some cases is presumably due to a slightly different distribution of muscle weakness in these individuals during development. The same could apply to the history of recurrent dislocation of the patellæ in several members of two families with type I HMSN.

Additional clinical features such as optic atrophy (McLeod, Low and Morgan, 1978), pupillary abnormalities (André-Van Leeuwen, 1943; Salisachs and Lapresle, 1977), pigmentary retinal degeneration (Massion-Verniory, Dumont and Potvin, 1946), deafness (Satya-Murti, Cacace and Hanson, 1979) and optic atrophy and deafness (Rosenberg and Chutorian, 1967; Iwashita, Inoue, Araki and Kuroiwa, 1970) have been described in association with classical peroneal muscular atrophy, but were rare in this series. They were not concordant within families. Their infrequency may be ascribed to the exclusion of complex syndromes in index cases. Some may be chance associations.

SUMMARY

Observations have been made on a series of 228 patients with hereditary motor and sensory neuropathy, comprising 120 index cases and 108 affected relatives. These could be separated into genetically distinct type I and type II categories depending upon whether motor nerve conduction velocity in the median nerve was below or above 38 m s^{-1}. These disorders constitute separate genetic subgroups within the clinical spectrum of 'peroneal muscular atrophy'.

Type I cases were more numerous. Most were of autosomal dominant inheritance, but a proportion were sporadic. Four families with probable autosomal recessive inheritance were identified; these displayed significantly slower motor conduction velocity. There was a positive correlation between motor conduction velocity in the propositi and that in their relatives in the total type I group which persisted after the autosomal recessive cases had been extracted, indicating further genetic heterogeneity amongst the autosomal dominant families. No X-linked recessive families were encountered.

Type I cases had a peak age of onset of symptoms during the first decade of life. In comparison with the type II cases, they displayed a greater tendency to show weakness of the hands, upper limb tremor and ataxia, generalized tendon areflexia and more extensive distal sensory loss, sometimes with acrodystrophic changes. Foot and spinal deformities were more frequent, probably due to the earlier age of onset. Nerve thickening was confined to the type I cases.

The onset of symptoms was most often in the second decade in the type II cases, but in some it was delayed, even as late as the seventh decade. Most cases were again of autosomal dominant inheritance, but two probable autosomal recessive families were detected, as well as sporadic cases. Upper limb tremor also occurred in this form but was considerably less common.

In both types, males tended to be more severely affected, and asymptomatic affected family members ('*formes frustes*') were more commonly female.

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COURSE AND PROGNOSIS OF MULTIPLE SCLEROSIS ASSESSED BY THE COMPUTERIZED DATA PROCESSING OF 349 PATIENTS

by C. CONFAVREUX, G. AIMARD *and* M. DEVIC

(From l'Hôpital Neurologique de Lyon, B.P. Lyon Montchat, 69394 Lyon Cedex 3)

CASES of multiple sclerosis (MS), collected in a neurological centre over a twenty-year period (1957-1976), have been re-examined. The purpose was not to restate the already known clinical description of the disease but, by analysis of the data of a large number of patients, to obtain a general view of the disease and to identify clinical, biological and genetic characteristics which may serve as markers to the eventual course of the disease.

Case Selection and Data Collection

Most cases of suspected multiple sclerosis living in the region were referred to the neurological centre and all cases known to the department were included in the survey. The majority of the patients had been admitted to hospital at least once and most patients were seen as outpatients on average twice a year. In those cases who were lost to follow-up only the information up to their last visit was used. No time limit was imposed on the delay from the first symptoms of the disease to the first attendance at hospital. Clinical examination and interview were performed by a limited number of doctors to ensure a uniform description of the signs and symptoms.

In this study the technique of computerized data processing was used which has been used in a limited number of other series. Alexander (1951) described a method based on invalidity scoring and neurological examination. Fog (1965*a*) using neurological examination at regular intervals was able, after plotting the initial points for each patient, to extrapolate the course of the disease acting as the basis for therapeutic evaluation. Poser and Hauptvogel (1973) described a system where clinical data could be fed directly into a computer but this has not yet been used in a longitudinal study (Poser, 1978).

The document sheets of the present study were divided into several parts: the first part contained the medical history including hereditary, social and personal details, and the onset and classifications of the various aspects of the disease; the second part was concerned with the relapses including triggering events, duration, severity, localization in the neuraxis, treatment and degree of recovery; the third part was devoted to the non-reversible basic state describing the functional impairment and nervous structures involved; the fourth part contained the cerebrospinal fluid (CSF) results and histocompatible antigen analysis (HLA); the fifth part described the treatment.

The data was processed by an Iris 60 C 11-HB computer which performed the various statistical analyses.

TABLE 1. DIAGNOSTIC CLASSIFICATION OF MULTIPLE SCLEROSIS. CRITERIA USED FOR DIAGNOSIS

Clinical data[1]	*Paraclinical data*
C1: Dissemination in SPACE (Neuraxis and optic nerve)	Acquired dyschromatopsia without clinically patent antecedent retrobulbar optic neuritis Retinal periphlebitis
C2: Dissemination in TIME	
	C3: Biology CSF protein alterations At least one of following: —moderate pleiocytosis + $\gamma G/TP$[2] > 10 per cent —$\gamma G/TP > 14.5$ per cent —oligoclonal distribution

[1] For details, *see* MacAlpine, 1961.

[2] $\gamma G/TP$ = gammaglobulins to total proteins quotient.

CLASSIFICATION

$$\text{Definite} = \text{C1} + \begin{cases} \text{C2}+\text{C3} \\ \text{or C2} \\ \text{or C3} \end{cases}$$

Probable = C1 alone
or C3 alone or with C2
Possible = C1 and C3 absent

Diagnostic Criteria

The diagnostic categories were based on those of MacAlpine (1961) with definite, probable and possible groups (Table 1). The criteria for diagnosing a demyelinating lesion were, however, somewhat modified. Acquired dyschromatopsia (Zeller, 1967) was used as evidence of optic neuritis but temporal pallor alone was not. Retinal periphlebitis (Rucker, 1944; Haarr, 1963; Möller and Hammerberg, 1963) was not evidence of optic neuritis but of one lesion or 'plaque'. Abnormalities of the caloric test and electronystagmogram were thought too inaccurate to diagnose a central vestibular lesion on their own. Visual evoked potentials (McDonald and Halliday, 1977) and computer axial tomography were not available during this study. Consideration was also given to the patient's age, familial occurrence and temporary aggravation of symptoms during hyperthermia.

Abnormalities of the CSF were also used and a positive CSF would advance a patient into a higher diagnostic group, that is, from possible to probable. A positive CSF was: a moderate mononuclear pleocytosis (5 to 50 cells) with gamma globulins over 10 per cent of total protein; gamma globulins over 14.5 per cent of the total protein; an oligoclonal distribution of gamma globulins on electrophoresis.

Four hundred and seventy-one cases were provisionally registered as multiple sclerosis from 1957 to 1976 and 349 of these could be reliably diagnosed according to the stated criteria: 173 cases (50 per cent) were 'definite', 105 cases (30 per cent) 'probable' and 71 cases (20 per cent) 'possible'. There were no cases of optic neuromyelitis using the original definition (Devic, 1894; Gault, 1894). At the close of the survey (June, 1976) the mean period of follow-up was 9.0 years and the mean delay from onset to first examination was 4.7 years.

Of the 349 patients, 140 were male (40 per cent) and 209 female (60 per cent), this difference being statistically significant ($\chi^2 = 13.64$, $P < 0.01$). The female preponderance was not explicable by the sex imbalance in the general population or by a bias in referral to the hospital. A similar female predominance has been shown in other studies (Müller, 1949; MacAlpine, 1961; Bonduelle and Albaranes, 1962; Leibowitz and Alter, 1973).

The mean age at onset in the present survey was 31.31 years (SD ± 10.06 years). In 10 per cent the onset was before the age of 20 years, in 70 per cent from ages 20 to 40 years, and in 20 per cent after the age of 40 years. This distribution was similar to the study of MacAlpine (1961) and Bonduelle and Albaranes (1962), but more restricted than that of Leibowitz and Alter (1973) and generally older than that of Müller (1949).

The age at onset was different in the two sexes with a mean of 29.4 years (±8.8) in males and 32.6 years (±10.6) for females. There was a significantly greater incidence of the disease in females over the age of 40 years ($\chi^2 = 7.04$, $P < 0.01$). Previous studies had shown this later onset in females (Ipsen, 1950; Poser, 1978) but others had shown the opposite trend (Müller, 1949; MacAlpine, 1961; Leibowitz and Alter, 1973).

Remittent and Progressive Phases of the Disease

'Relapses' and 'progression' were the two basic events occurring during the course of the disease. Relapses were characterized by either the rapid appearance of new symptoms or the sudden worsening of old symptoms, lasting longer than twenty-four hours and occurring at least one month after the preceding relapse.

Relapses could be further classified into 'pure relapses' with a complete regression of symptoms and 'relapses with sequelæ' with lasting symptoms of a chronic disability grading of 2 or more (MacAlpine, 1961). The transient neurological symptoms at the time of hyperthermia were not classified as relapses. Following a relapse there was a complete or partial regression of the symptoms to a stable state which did not alter until the next relapse. This phase of the illness was called the 'remittent phase'. The 'progressive phase' or 'progression' was defined as the absence of a stable phase and a steadily worsening condition whether supervened by relapses or not.

Three types of clinical course could be defined: (1) remittent type with a stable phase between relapses throughout the duration of the illness; (2) remittent-progressive type with an initial remittent phase followed by the progressive phase; and (3) progressive type with no stable phase but the illness commencing with the progressive phase.

Type	*No. of patients*	*Mean age at onset*	*No. of patients (%) for each class of age at onset*											
R – – –	202	29.2	0	1	13	25	18	17	10	9	3	2	0.5	0.5
RP ——	83	31.7	1	4	6	15	17	25	12	10	5	5	1	0
P ——	64	37.3	0	0	2	6	14	20	23	14	6	11	2	2

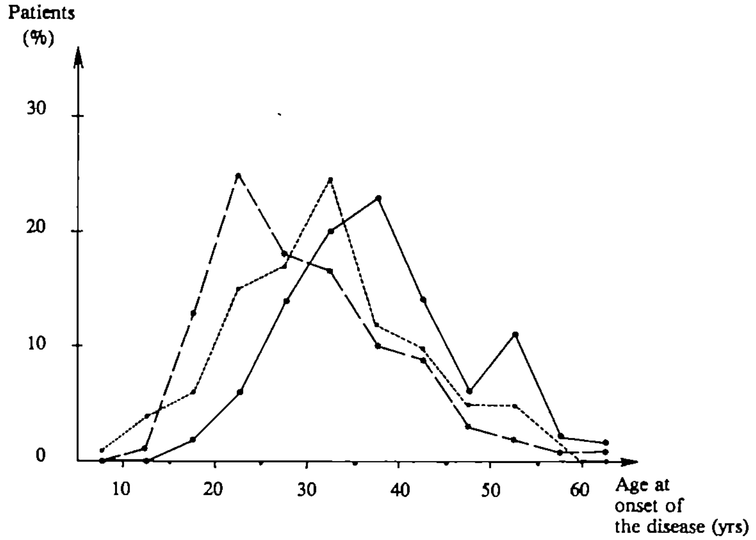


FIG. 1. Age at onset of three types of MS. R = remittent type. RP = remittent progressive type. P = progressive type.

Although the rationale for this system might have been questioned, it was thought useful since much of the data was retrospective and subject to the inaccuracy of recall by the patient.

In the study there were 202 patients (58 per cent) of the remittent type, 83 patients (24 per cent) of the remittent-progressive type and 64 patients (18 per cent) of the progressive type. There was no relation to the sex of the patient.

The age at onset was 29.2 years (±9.2) for the remittent type, 31.7 years (±10.2) for the remittent-progressive type and 37.3 years (±9.9) for the progressive type. There was no statistical difference in the age at onset, both expressed by mean values and by distribution, for the remittent and remittent-progressive types but there was for the progressive type. The mean age at onset for the two types with a remittent onset was 30.0 years compared with the progressive type of 37.3 years. The mean duration of the illness for the remittent type was 7.6 years (±7) and that of the remittent-progressive type 13.3 years (±8.3). This was an argument for considering remittent-progressive forms of multiple sclerosis as remittent forms of multiple sclerosis which have had 'time to grow older'. This was also the finding of Fog and Linnemann (1970) and Leibowitz and Alter (1973).

TABLE 2. AGE AT ONSET OF PURE RELAPSES DURING THE COURSE OF MS

	Age at onset of pure relapse (yrs)		
Course of MS	*Mean*	*SD*	*Variance analysis*
PR	28.7	± 9.0	n.s.
PR-RS	28.3	± 9.2	
PR-P	30.9	±10.9	
PR-RS-P	30.1	± 6.4	
All types	29.2	± 9.4	

PR = pure relapse. RS = relapse with sequelæ. P = progressive phase. SD = standard deviation. n.s. = not significant.

There was no statistical difference in the age at onset of pure relapses, whether followed by pure relapses, relapses with sequelæ or the progressive phase. Likewise there was no difference in the age at onset of relapses with sequelæ, whether preceded by pure relapses or not, or whether followed by the progressive phase or not. Similarly there was no difference in the age at onset of the progressive phase whether starting *de novo* or preceded by the remittent phase. Moreover the mean ages at onset for these three stages were significantly different from each other (variance analysis $P < 0.001$).

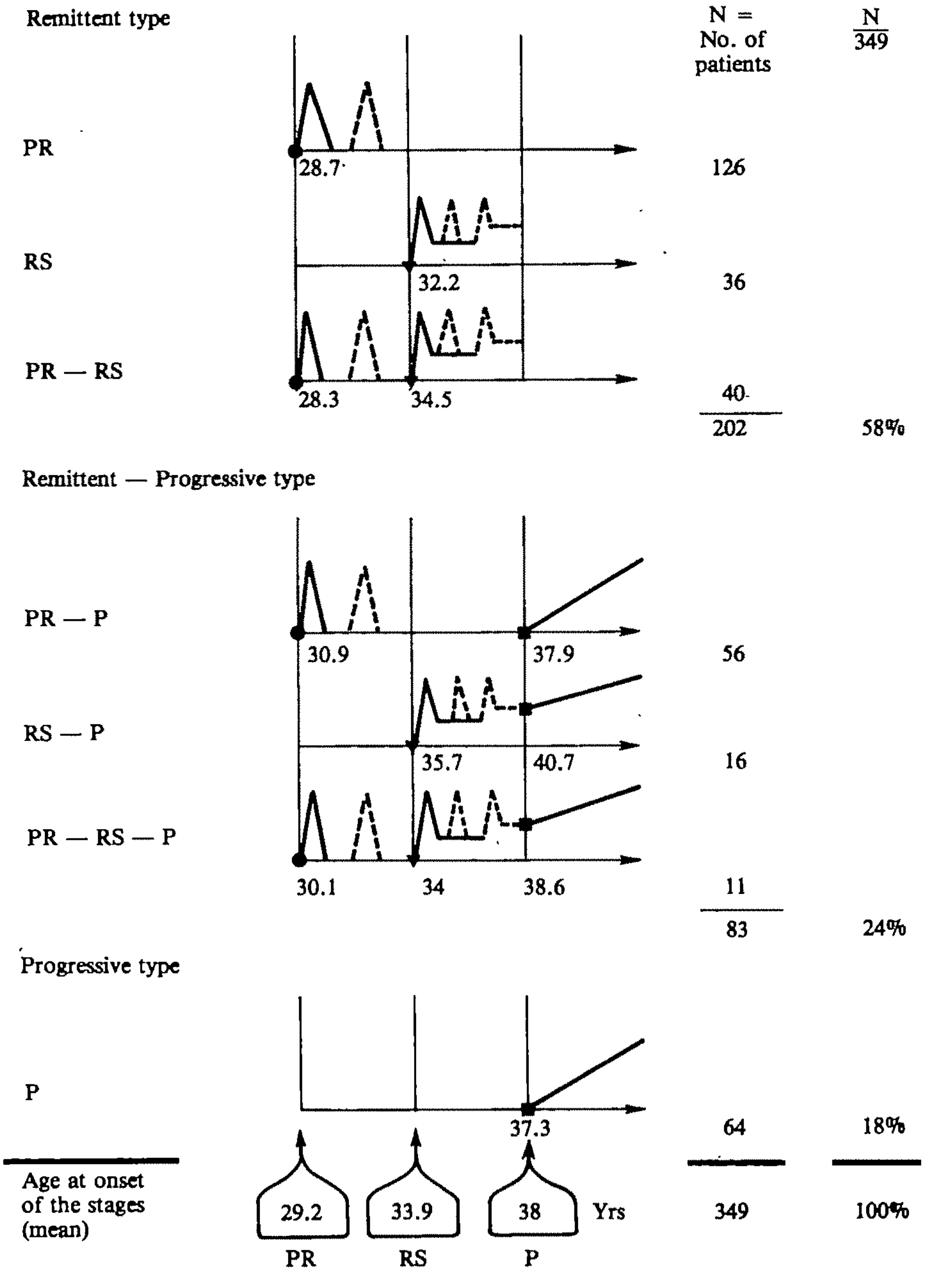


FIG. 2. Age at onset of the different stages during the course of MS. PR = pure relapse. RS = relapse with sequelæ. P = progressive phase.

TABLE 3. AGE AT ONSET OF RELAPSES WITH SEQUELÆ DURING THE COURSE OF MS

Course of MS	*Age at onset of relapses with sequelæ (yrs)*		*Variance analysis*
	Mean	*SD*	
RS	32.2	± 9.6	n.s.
PR-RS	34.5	±10.1	
RS-P	35.7	± 8.6	
PR-RS-P	34.0	± 6.2	
All types	33.9	± 9.3	

For abbreviations *see* Table 2.

Only the relapses in the remittent phase were studied since those of the progressive phase were difficult to identify. The probability of a fresh relapse was highest immediately following a relapse and then fell exponentially.

The interval between consecutive relapses tended to shorten and was not related to sex of the patient, remittent or remittent-progressive type of disease, or with age at onset. The increasing frequency of relapses was in agreement with some previous studies (Bonduelle and Albaranes, 1962; Lhermitte, Marteau, Gazengel, Dordain and Deloche, 1973) and contrasted with others (Müller, 1949; MacAlpine, 1961; Leibowitz and Alter, 1973).

The frequency of relapses was calculated, in the remittent type from the interval between the first and last relapse and the total number of relapses minus one, and in the remittent-progressive type from the duration of the remittent phase and the total number of relapses during it. In the 147 patients of the remittent type the

TABLE 4. AGE AT ONSET OF THE PROGRESSIVE PHASE DURING THE COURSE OF MS

Course of MS	*Age at onset of progressive phase (yrs)*		*Variance analysis*
	Mean	*SD*	
P	37.3	± 9.9	n.s.
PR-P	37.9	±10.2	
RS-P	40.7	± 7.1	
PR-RS-P	38.6	± 5.1	
All types	38.0	± 9.5	

For abbreviations *see* Table 2.

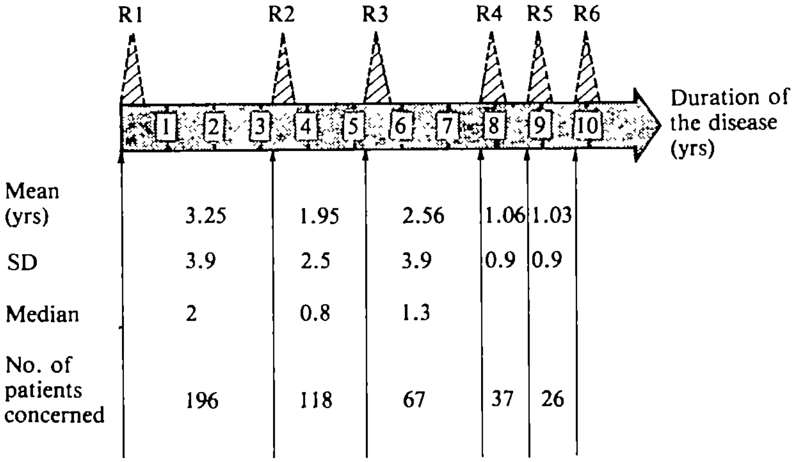


FIG. 3. Interval between relapses during the remittent phase. SD = standard deviation. R = numbered relapse.

frequency was 0.95 ± 1.0 relapses per year and in the 82 patients of the remittent-progressive type the frequency was 0.69 ± 0.7. The overall frequency of the remittent phase was 0.86 relapses per year. There was no correlation with age at onset and sex. The actual mode of calculation of relapse rate was important since if all the known relapses, including those of the progressive phase, of all the patients for all the years of illness were counted there would be 837 relapses in 2670 years giving a rate of 0.31 relapses per year. A comparison with previous studies showed the relapse rate in this series was among the higher recorded (Alexander, Berkeley and Alexander, 1958; Fog and Linnemann, 1970; MacAlpine, Lumsden and Acheson, 1972; Lhermitte *et al.*, 1973; Thygesen, 1955).

TABLE 5. INTERVAL BETWEEN THE FIRST TWO RELAPSES (R1 R2) AND THE AGE AT ONSET OF DISEASE

Age at onset (yrs)	*No. of patients*	*R1 R2 (yrs)*	
		Mean	*SD*
< 20	31	3.8	±4.2
20–40	144	3.1	±3.8
> 40	21	3.2	±3.7

In this series the age at onset of the progressive phase was 38 years among the 147 patients so affected. For the 83 patients of the remittent-progressive type the period before the onset of the progressive phase was 6.8 years (±5.4). This period was not affected by sex, but was closely related to the age at onset of the disease, progression occurring more quickly with later onset of the disease (Variance analysis $P < 0.001$; correlation rate $r = -0.44$, $P < 0.01$).

TABLE 6. AGE AT ONSET OF MS IN REMITTENT-PROGRESSIVE TYPES AND THE PERIOD BEFORE ONSET OF THE PROGRESSIVE PHASE

Age at onset of MS (yrs)	*No. of patients*	*Mean period before progressive phase (yrs)*
< 20	9	9.7
20–30	26	8
30–40	31	6.8
40–50	12	3.8
50–60	5	2.2
> 60	0	—

In the remittent-progressive type of multiple sclerosis the period before the onset of the progressive phase was also related to the interval between the first two relapses, whether sequelæ followed these relapses or not (Variance analysis $P < 0.001$).

TABLE 7. INTERVAL BETWEEN THE FIRST TWO RELAPSES (R1 R2) AND THE PERIOD BEFORE ONSET OF THE PROGRESSIVE PHASE

R1 R2 interval (yrs)	*No. of patients*	*Mean period before onset of progressive phase (yrs)*
< 0.5	7	4.5
0.5– 1.5	15	5.7
1.5– 2.5	7	6.2
2.5– 3.5	5	7.5
3.5– 4.5	5	7.8
4.5– 5.5	4	9.8
5.5–10.5	6	12.2
10.5–15.5	2	21.4
> 15.5	0	—

From the number of patients in the progressive phase at any one time compared to the total number of patients an actuarial analysis demonstrated that 18 per cent of patients started their illness in the progressive phase, 30 per cent entered the progressive phase by five years and 50 per cent by eleven years. The influence of age at onset was clear from the graph.

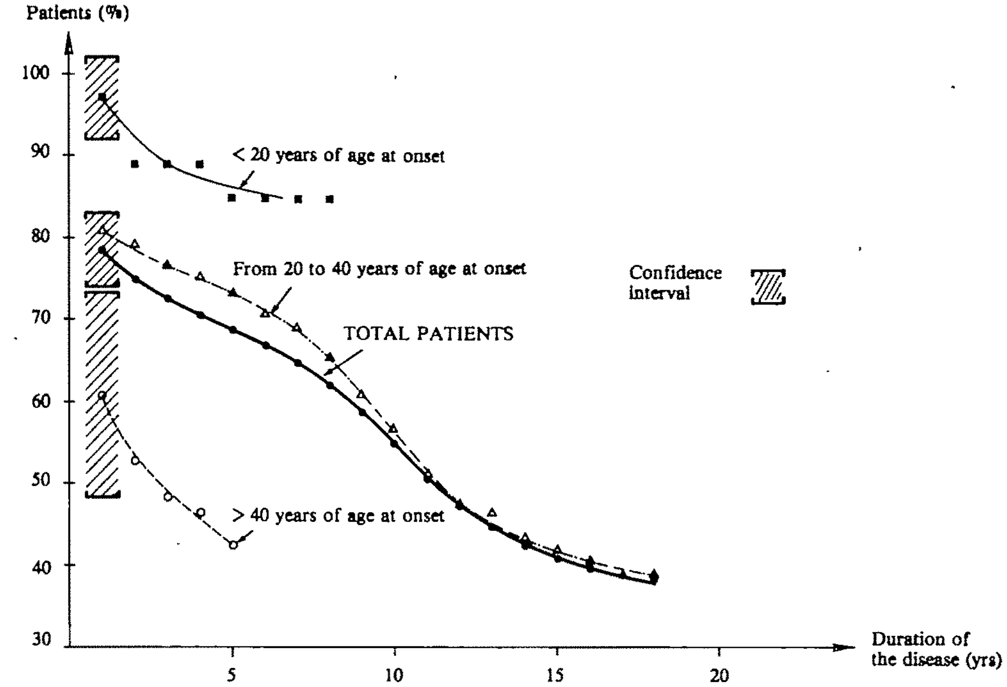
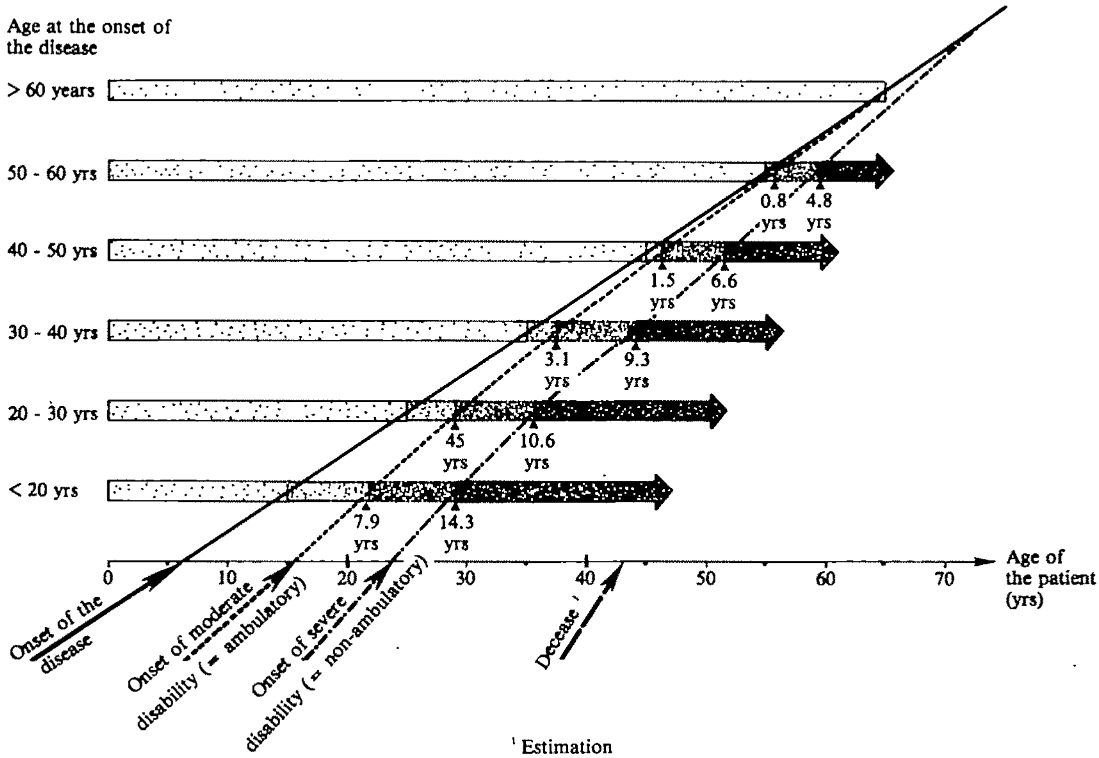


FIG. 4. Actuarial curve for onset of the progressive phase. The ordinate represents the percentage of patients with MS not in the progressive phase. *Confidence intervals* (hatched): for upper curve, ± 5.0; for middle curves, ±4.5; for lower curve, ±12.0.

Functional Outcome

The method of scoring the non-reversible functional state was based on the groupings of MacAlpine, Compston and Lumsden (1955) with three basic groups: no disability (Grades 0–1); moderate disability, still ambulatory (Grades 2–3); and severe disability, not ambulatory (Grades 4–6). When assessing the disability no account was taken of the treatment since steroids were thought to have little long-term effect (Fog, 1965*b*; Millar, Vas, Naronha, Liversedge and Rawson, 1967; MacAlpine *et al.*, 1972) and few patients received long-term azathioprine treatment.



' Estimation

FIG. 5. Age at onset of MS and the functional outcome.

There were 194 patients who were moderately disabled and 50 per cent were so in the first year of illness. There was no difference in males and females. The interval from onset of the disease to moderate disability was 3.45 years (±5.2) for all types of patients. In the progressive types the interval was only 0.34 years, in the remittent type 4.0 years and in the remittent-progressive type 5.5 years. There was a strong correlation of the age at onset of the disease with the interval to moderate disability ($P < 0.001$); an interval of eight years with the age of onset at 20 years and one year with onset at 50 years (*see* fig. 5). The actuarial graph showed that 30 per cent of patients were moderately disabled at the onset of disease, 50 per cent after six years' illness and 75 per cent after 15 years (*see* fig. 6).

Ninety patients were severely disabled with no difference in males or females. The interval from the onset of the disease to severe disability was 9.5 years (±7.4) for all patients, 5.8 years (±3.0) for the 25 patients of the progressive type, 11.4 years (±11.3) for the 6 patients of the remittent type and 10.9 years (±7.6) for the 59 patients of the remittent-progressive type. The age at onset was strongly correlated with the interval before severe disability ($P < 0.025$) with an interval of 14.3 years with onset aged 20 years and interval of 4.8 years with onset aged

50 years (*see* fig. 5). The actuarial curve showed 10 per cent of patients were severely disabled after five years, 25 per cent after ten years and 50 per cent after eighteen years (*see* fig. 6).

In the cases that died the mean duration of survival was 10.75 years, (±5) being longer for the 7 females (13.1 years) than for the 13 males (9 years). The actuarial graph showed that 10 per cent of patients died within fifteen years and the mean survival would be about thirty years. This was in agreement with other surveys (MacLean and Berkson, 1951; MacAlpine *et al.*, 1972).

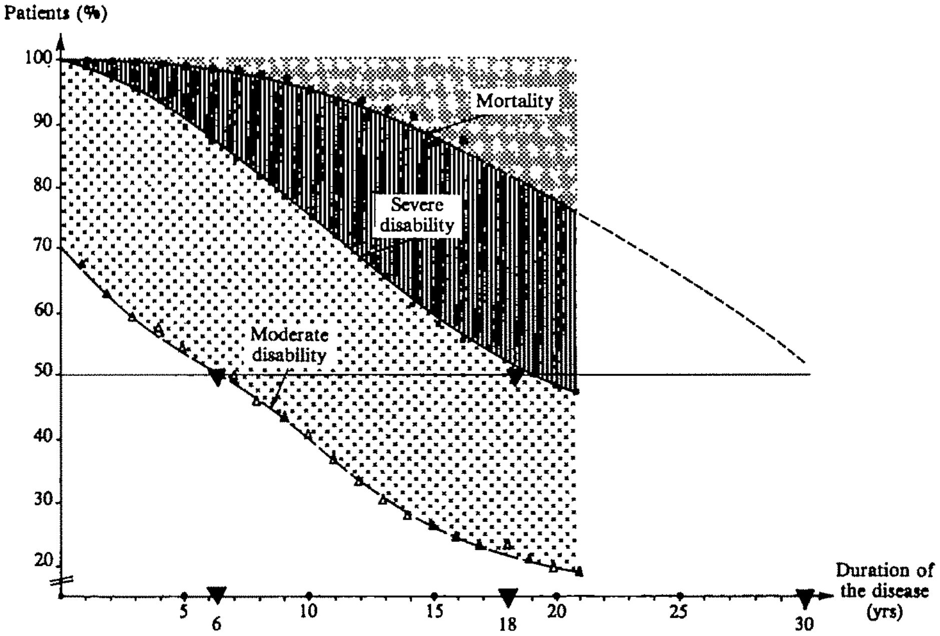


FIG. 6. Actuarial curve of functional outcome and duration of disease for 349 patients. The ordinate represents the percentage of patients with MS not moderately disabled or severely disabled or dead.

Factors Affecting Prognosis

The disability score and duration of disease were combined to define various forms of the disease. The 'benign' form had no disability after ten years or a moderate disability after fifteen years. 'Hyperacute', 'acute', 'subacute', 'intermediate' forms had severe disability with a duration of disease of less than five years, five to ten years, ten to fifteen years and more than fifteen years, respectively. 'Non-classified' forms had no disability or moderate disability but follow-up was too short to accurately estimate the outcome.

TABLE 8. DEFINITION OF VARIOUS FORMS OF DISABILITY

Period of time (yrs)	*Disability* *None (Grades 0 and 1 of MacAlpine)*	 *Moderate (Grades 2 and 3)*	 *Severe (Grades 4, 5 and 6)*
< 5	1	6	11
5–10	2	7	12
10–15	3	8	13
15–20	4	9	14
> 20	5	10	15

Period of time:
Duration of the disease

Period of time:
Period before onset
of severe invalidity

The compartments numerated:

3, 4, 5, 9 and 10	correspond to the 'Benign' forms
1, 2, 6, 7 and 8	correspond to the 'Non-classified'
11	correspond to the 'Hyperacute'
12	correspond to the 'Acute'
13	correspond to the 'Subacute'
14 and 15	correspond to the 'Intermediate'

The incidence of 'benign' forms is far from negligible in our series. They have been discussed extensively by MacAlpine (1961), Lehoczky and Halasy-Lehoczky (1963), Bonduelle (1967) and MacKay and Hirano (1967).

TABLE 9. NUMBER OF PATIENTS AND THE FORMS OF MS

	Forms of multiple sclerosis *Benign*	 *Non-classified*	 *Hyperacute*	 *Acute*	 *Subacute*	 *Intermediate*	 *Total*
No. of patients	50	209	29	27	19	15	349
Total %	14.3	59.9	8.3	7.7	5.4	4.4	100

The number of relapses in the remittent phase had an interesting relation to the outcome, the 'benign' forms having a greater number of relapses (Variance analysis $P < 0.001$).

TABLE 10. THE NUMBER OF RELAPSES IN THE REMITTENT PHASE AND THE FORMS OF MS

	Forms of multiple sclerosis					
	Benign	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*
Mean No. of relapses	4.1 ±2.7	2.4 ±1.8	2.2 ±1.6	3 ±2.2	2.8 ±2.2	2.2 ±1.0
No. of patients	46	174	16	18	16	15

The interval between the first two relapses had a significant relationship to the outcome of the disease ($P < 0.001$); the shorter the interval the poorer the prognosis. This was in agreement with other studies (MacAlpine, 1961; Bonduelle and Albaranes, 1962; Riser, Geraud, Rascol, Benazet and Segria, 1971). A similar relationship held for later relapses.

TABLE 11. INTERVAL BETWEEN THE FIRST TWO RELAPSES (R1 R2) AND THE FORMS OF MS

	Forms of multiple sclerosis					
	Benign	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*
Mean R1 R2 interval (yrs)	6.2 ±5.6	2.1 ±1.9	0.9 ±1.0	2.4 ±1.3	3.7 ±3.5	6.6 ±5.8
No. of patients	42	109	9	15	11	10

In comparing the type of multiple sclerosis and the outcome, the progressive type had a much worse prognosis ($\chi^2 = 177$, $P < 0.001$). There were three times more hyperacute cases in the progressive type than the remittent onset type.

TABLE 12. THE PERCENTAGE OF THE TYPES OF MS IN THE DIFFERENT FORMS OF THE DISEASE

	Forms of multiple sclerosis						
Type of MS	*Benign*	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*	*Total*
Remittent (n = 202)	20	77	1	0.5	1	0.5	100
Remittent-progressive (n = 83)	6	23	17	20	17	17	100
All with remittent onset (n = 285)	16	61	6	6	6	5	100
Progressive (n = 64)	6	55	20	14	5	0	100

In the remittent-progressive type of disease there was a correlation with the interval before the onset of the progresssive phase and the outcome ($P < 0.001$). In this type of multiple sclerosis more than half the cases were severely disabled within fifteen years.

TABLE 13. THE INTERVAL BEFORE THE ONSET OF THE PROGRESSIVE PHASE AND THE OUTCOME IN THE REMITTENT-PROGRESSIVE TYPE OF MS

	Forms of multiple sclerosis					
	Benign	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*
Mean interval before onset of progression (yrs)	10.6 ±3.7	4.3 ±3.4	1.7 ±1.1	6.0 ±3.9	8.4 ±3.4	13.3 ±6
No. of patients	5	19	14	17	14	14

There was no sex difference in the outcome of the disease ($\chi^2 = 0.093$). This fact could be used as evidence against a relationship of pregnancy to severity of disease. This was in agreement with the studies of Thygesen (1955) but contradictory to the studies of Müller (1949) and MacAlpine (1961) who found more severe disease in females, and of studies of Leibowitz and Alter (1973) who found more severe disease in males.

The age at onset of the disease had a high correlation with the outcome ($P < 0.001$). The older the age at onset the faster was its course. This was in agreement with other studies (Müller, 1951; Thygesen, 1955; MacAlpine, 1961; Bonduelle, 1967).

TABLE 14. THE AGE AT ONSET AND THE FORM OF MS

	Forms of multiple sclerosis					
	Benign	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*
Mean age at onset (yrs)	27.6 ±7	31.7 ±10.4	35.7 ±10.3	34.1 ±9.2	29.2 ±7.2	26.6 ±11.4
No. of patients	50	209	29	27	19	15

The symptomatology of the initial relapse of the remittent phase had no prognostic value.

The mode of onset of the progressive type had no prognostic value.

It was found that during the course of the disease the relative frequency of relapses involving the sensory and motor long tracts and cerebellar system

TABLE 15. SYMPTOMATOLOGY OF THE 289 INITIAL RELAPSES AND THE FORM OF MS

Symptom of initial relapse	*Forms of multiple sclerosis*						
	Benign	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*	*Total*
LE	15	60	6.5	7	4	7	100
UE	10	74.5	3	7	3	3	100
SS	21	64.5	7.5	3	1.5	2.5	100
SP	5.5	50	11	16.5	5.5	11	100
VI	17	65	3	5.5	7	3	100
BS	12	66.5	5.5	6.5	6.5	2.5	100

All the initial relapses were included whether mono or plurisymptomatic. The distribution of each type of symptom among the various forms of MS was expressed as a percentage. LE = lower extremity dysfunction. UE = upper extremity dysfunction. SS = sensory disturbance. SP = sphincter disturbance. VI = visual dysfunction (optic neuritis). BS = brain-stem dysfunction.

TABLE 16. SYMPTOMATOLOGY OF 150 MONOSYMPTOMATIC INITIAL RELAPSES AND THE FORM OF MS

Symptoms of initial relapse	*Forms of multiple sclerosis*						
	Benign	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*	*Total*
LE	13.5	43·5	6.5	10	6.5	20	100
SS	26.5	56	12	3	0	3	100
VI	13	66	2	6.5	10.5	2	100
BS	13.5	53.5	10	10	6.5	6.5	100

The distribution of each symptom among the various forms of MS was expressed as a percentage. Upper extremity and sphincter dysfunctions were too infrequent for analysis.

TABLE 17. THE SYMPTOMATOLOGY OF THE ONSET OF THE PROGRESSIVE TYPE IN 64 PATIENTS AND THE OUTCOME OF THE DISEASE

Symptoms of onset of progression	*Forms of multiple sclerosis*						
	Benign	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*	*Total*
LE	6	53	20.5	15	6	0	100
UE	10.5	47.5	21	16	5.5	0	100
SS	0	62	24	9.5	5	0	100
SP	6	59	17.5	17.5	0	0	100

The distribution of each symptom among the various forms of MS was expressed as a percentage. Visual and brain-stem dysfunction were too infrequent for analysis.

increased whilst those of the cranial and optic nerves decreased. It could be concluded that the risk of producing lasting sequelæ or triggering the progressive phase was greater with relapses of the former structures than the latter. This was understandable by the relative space occupied by these systems in the neuraxis.

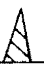
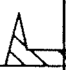
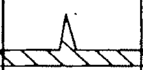
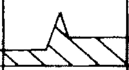
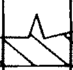
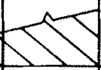
		Relapses							*Onset of progressive phase*
			Remittent phase				*Relapses of progressive phase*		
				Relapses with sequelæ					
		All relapses	*Pure relapses*	*Initial*	*Subsequent non-worsening*	*Subsequent worsening*	*Initial*	*Sub-sequent*	
									
No.		837	544	113	83	37	38	14	147
Distribution of symptoms expressed as percentage	LE	48	37	68	60	73	95	43	82
	UE	28	22	32	40	49	47	21	32
	SS	46	49	44	36	32	42	2	35
	SP	10	4	24	7	24	45	21	33
	VI	22	21	29	24	30	5	14	6
	BS	24	27	12	22	16	24	50	18
Total		178	160	209	189	224	258	156	206

FIG. 7. Symptomatology of the different types of relapse and the onset of progression. The distribution of symptoms is expressed as a percentage of the number of relapses in each particular group. As many relapses were polysymptomatic, the total is greater than 100 per cent. In the category 'relapses with sequelæ' inclusion in the 'worsening' group indicates that the subsequent disability was greater than before the relapse, while in the 'non-worsening' group the disability was the same as before the relapse. The symptoms at the onset of the progressive phase include those cases (109) commencing insidiously and those commencing the progressive phase with a relapse (38). The diagrammatic representation of the relapses has time as the abscissa and disability as the ordinate in non-specified units. LE = lower extremity dysfunction. UE = upper extremity dysfunction. SS = sensory symptoms. SP = sphincteric dysfunction. VI = visual dysfunction. BS = brain-stem dysfunction.

Four hundred and two lumbar punctures were performed in 298 patients. There was no correlation of the outcome to the cell count or the total protein; 141 patients had CSF examined for gamma globulins at least once and using the first value for each patient, an increased gamma globulin and gamma globulin/total protein ratio was associated with a poor outcome. However, this association may have been explained by the age distribution of the patients who were older than the

TABLE 18. CSF CONSTITUENTS AND DIFFERENT FORMS OF MS

	Forms of multiple sclerosis						
	Benign	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*	*Variance analysis*
No. of patients	11	105	12	5	5	3	
Mean cell count C/mm³	6.8	5.5	5.3	7	4.9	2.8	n.s.
Total protein g/l	0.4	0.4	0.42	0.38	0.43	0.41	n.s.
Albumin g/l	0.198	0.272	0.214	0.286	0.252	0.241	n.s.
Gamma globulins g/l	0.037	0.059	0.105	0.075	0.102	0.061	$P < 0.05$
Gamma globulins/total protein ratio per cent	12	13.5	19.5	19	20	14.5	$P < 0.025$

C/mm³ = cells per cubic millimetre.

mean. On the whole lumbar puncture data had little prognostic value. Thirty-three patients received steroid therapy in the preceding month and 11 patients azathioprine therapy.

Sixty-four patients had the A and B histocompatible antigens estimated and there were 13 patients with A3, 11 with B7 and 10 with A3 and B7. Such a sample was too small for statistical analysis.

TABLE 19. THE HISTOCOMPATIBLE ANTIGENS A3 AND B7 AND FORMS OF MS

	Forms of multiple sclerosis					
	Benign	*Non-classified*	*Hyperacute*	*Acute*	*Subacute*	*Intermediate*
Serotype						
A3	1	9	1	0	0	2
B7	1	4	3	1	1	1
A3 and B7	1	4	1	2	0	0

SUMMARY

The information of 349 cases of multiple sclerosis, seen in a neurological department over a twenty-year period and followed up for a mean of nine years, was analysed by computerized data processing. The mean age at onset was 30.0 years for the remittent onset types (82 per cent cases) and 37.3 years for the progressive onset types (18 per cent cases). During the course of the disease the age of the 'pure relapse' stage was 29.2 years, of the relapse with sequelæ stage 33.9 years and of the progressive phase 38.0 years. The interval between the first two relapses in the remittent-progressive type was important, the shorter the interval the sooner the progressive phase occurred. The relapses tended to increase in frequency before the progressive phase started.

Using an actuarial graph, 50 per cent of cases could be expected to be moderately disabled (still ambulatory) in six years, and severely disabled (not

ambulatory) in eighteen years and dead in thirty years. Combining a disability score and the duration of the disease prognostic factors could be studied. A late onset of the disease, a short interval between the first two relapses and the occurrence of the progressive phase were associated with a poor outcome. Sex of patient, the symptomatology of the initial relapses, and the constituents of the CSF had no prognostic value.

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A PHYSIOLOGICAL MECHANISM OF BRADYKINESIA

by MARK HALLETT *and* SHAHRAM KHOSHBIN

(*From the Department of Neurology, Harvard Medical School and the Section of Neurology, Department of Medicine, Peter Bent Brigham Hospital, Boston, Mass. 02115, USA*)

INTRODUCTION

ONE of the most striking features of the motor disability of patients with Parkinson's disease is bradykinesia. Bradykinesia has many different aspects including prolonged reaction time to initiate a movement (Draper and Johns, 1964; Barbeau and DeGroot, 1966; Brumlik and Bosches, 1966), prolonged time to arrest a false movement (Angel, Alston and Higgins, 1970), prolonged time to change a motor pattern (Joubert and Barbeau, 1969) and weakness, at least to the extent of rapid fatigue on prolonged tasks (Schwab, England and Peterson, 1959; Joubert and Barbeau, 1969). The most characteristic feature, however, is slowness of movement (Draper and Johns, 1964; Barbeau and DeGroot, 1966; Brumlik and Bosches, 1966; Joubert and Barbeau, 1969).

Normally, people are able to move their limbs with a continuous spectrum of velocities. The fastest movements are often called ballistic, even though these movements may just be at one end of the spectrum rather than qualitatively different from other slower movements. Bradykinesia must reflect itself in an abnormality of ballistic movements, and it is the purpose of this paper to define the underlying pathophysiology.

As the term 'ballistic movement' is used differently by different authors, it is necessary to specify its meaning in relation to this study. As recently summarized by Desmedt and Godaux (1978), following Richer (1895*a*, *b*) and Stetson and McDill (1923), the initial use of the term ballistic referred to those movements which are so brief that the agonist would cease firing before the end of the movement. Such movements were thought to be unmodifiable once set into action by virtue of their brevity. Other authors, such as Flowers (1975, 1976), have extended the meaning of ballistic to refer to any movement performed 'open-loop', without possibility of modification, even if taking a longer period of time.

We would prefer, as do Desmedt and Godaux (1978), to use ballistic more in the original sense, but to be defined electromyographically as fitting a characteristic pattern of activation. Wachholder and Altenburger (1926) first described the initial part of the electromyographic pattern of the most rapid movements as being triphasic with a burst of activity in the agonist, followed by a burst in the antagonist while the agonist is silent, followed by another burst in the agonist. These bursts of activity can be referred to as Ag 1, An 1 and Ag 2, respectively. This pattern has been repeatedly confirmed in both proximal (Hallett, Shahani and Young, 1975*a*) and distal muscles (Hallett and Marsden, 1979*a*, *b*). In the fastest movements the burst duration of the first agonist and first antagonist components are fixed independent of the distance of the movement (Freund and Büdingen, 1978; Hallett and Marsden, 1979*a*). Desmedt and Godaux (1977, 1978) have shown that these movements exhibit a different pattern of motor unit behaviour than slower, 'ramp' movements. Operationally, normal subjects and patients will produce ballistic movements with this physiological pattern if they are urged to make their movements as rapidly as possible. Thus, even weak patients with pyramidal tract or alpha motor neuron lesions, if they try to move as rapidly as possible, will produce triphasic patterns even if the movements are slower than those seen in normally strong subjects (Hallett, 1979*a*).

Flowers has made several important quantitative observations about bradykinetic movement in his studies of ballistic movements performed by patients with Parkinson's disease. In his first study step-tracking performance was analysed for both large and small displacements (Flowers, 1975). The short ballistic movements were accomplished with normal speed while larger ballistic movements were performed more slowly than normal. In a second study, this phenomenon was studied with a series of steps of different distance (Flowers, 1976). Normals accomplish each of the different steps in the same time period; longer movements are made with faster velocity. This is the consequence of the fact noted above that the durations of the first agonist and antagonist bursts are constant independent of distance; longer movements are made by increasing EMG activity within the set time of the burst (Hallett and Marsden, 1979*a*). Patients with Parkinson's disease made all the movements with constant speed, taking a longer time for longer movements.

In a previous study of patients with Parkinson's disease the EMG patterns of a sterotyped 10-degree rapid elbow flexion movement were analysed (Hallett, Shahani and Young, 1977). The patterns in the patients with Parkinson's disease were normal with respect to durations of the individual bursts and alternation of activity in the antagonist muscles. Many patterns appeared normal in all respects, but fairly often it was observed that the movement was not completed during the time of the triphasic pattern, but required the additional time of an additional cycle of alternating bursts in the biceps and triceps (fig. 1F in Hallett, Shahani and Young, 1977). If in patients with Parkinson's disease, short ballistic movements could be accomplished in the normal one cycle of the triphasic pattern, but longer ballistic movements require additional cycles, then all of Flowers' kinematic observations can be explained. The goal of this investigation was to show whether this physiological process of additional cycles could indeed be a mechanism of bradykinesia.

METHODS

In an experimental protocol approved by the Peter Bent Brigham Hospital Human Studies Committee, normal subjects and patients with Parkinson's disease gave informed consent to participate. There were 19 patients with Parkinson's disease, 12 men and 7 women, ranging in age from 47 to 82 years. They displayed varying degrees of disability and were being treated with different regimens. The normal subjects were laboratory personnel or neurological patients without known disorders of the motor system (for example, patients with back pain). There were 11 normal subjects, 6 men and 5 women, ranging in age from 30 to 83 years. In both patients and controls rapid elbow flexion movements of the dominant arm were studied.

The subject sat in a chair facing an oscilloscope (fig. 1). The arm was strapped into a light plastic splint with one section for the forearm and one for the upper arm. The two sections of the splint were joined together by a light metallic frame which had a hinge at the level of the elbow into which was incorporated a potentiometer. By means of the potentiometer, rotation of the elbow was converted into a variable voltage. Another part of the metal frame had a handle for the subject to grip which rotated the forearm into supination. (This is important so as to maintain biceps, rather than brachioradialis, as the chief flexor of the elbow). Movements were made in the horizontal plane by abducting the shoulder to 90 degrees by suspending the splint with wires attached to a hook on the ceiling. The splinting and suspending processes were comfortable and non-fatiguing.

The oscilloscope screen facing the subject displayed the voltage from the potentiometer as the height of the single beam which was running rapidly so to appear as a line. The graticule was illuminated and the lowest line of the graticule corresponded to an elbow angle of 120 degrees. The first line up from the bottom corresponded to 110 degrees, the second line up corresponded to 100 degrees, and the fourth line up, which was the middle of the graticule, corresponded to 80 degrees.

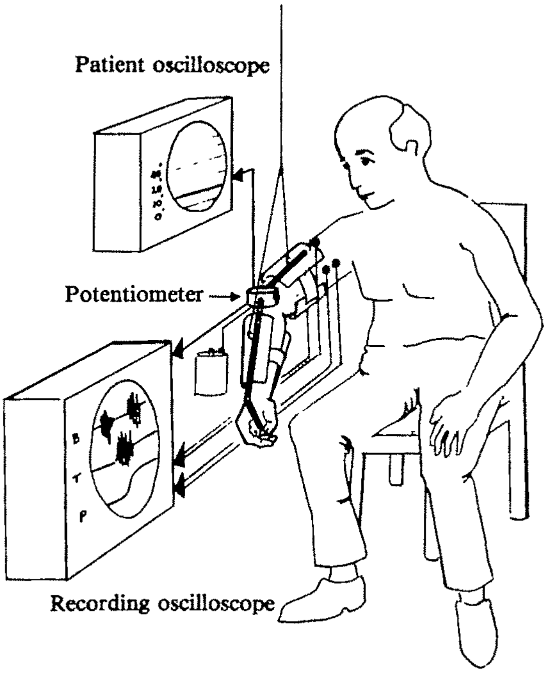

FIG. 1. A diagrammatic representation of the experimental set-up.

Subjects were asked to make rapid, accurate elbow flexion movements beginning at 120 degrees, with the line under their control superimposed upon the bottom of the graticule. Three movements of differing angular distance were studied, 10 degrees (to the first line up on the graticule), 20 degrees (to the second line up) and 40 degrees (to the fourth line up). Only well practised movements were studied and during the course of the experiment the subjects were constantly urged to move as rapidly as they could.

EMG with surface electrodes was recorded from biceps and triceps. EMG activity and elbow angle were recorded on moving light-sensitive paper with a TECA TE-4 electromyograph.

RESULTS

Ten of the 11 normal subjects were able to accomplish the three movements of different length with a single cycle of the triphasic pattern, Ag 1, An 1 and Ag 2 (fig. 2). EMG burst durations were relatively unchanged for movements of greater

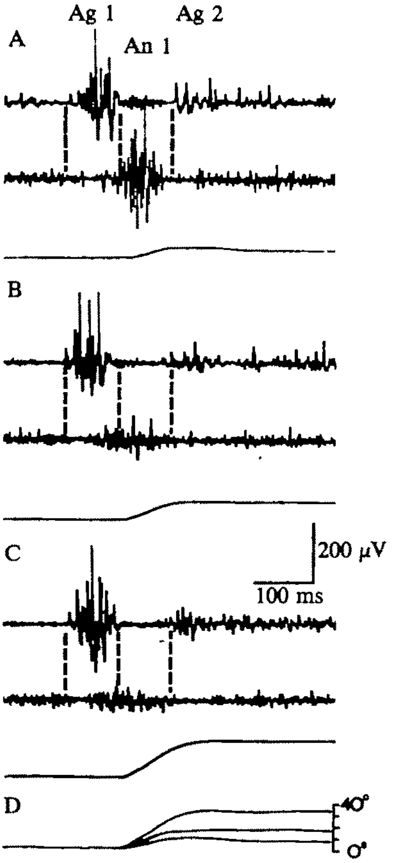

FIG. 2. Attempted ballistic movements of 10 deg (A), 20 deg (B) and 40 deg (C) by a normal 83-year-old woman. In A, B and C the traces are, from above downwards, biceps EMG, triceps EMG and position of the elbow. D shows the three position traces superimposed. The parts of the figure were aligned so that the movements all began at the same time from the beginning of the traces. The dashed vertical lines are discontinuous straight lines indicating the correspondence of the timing of EMG bursts in the different movements.

distance, but the amount of EMG activity within the bursts increased to provide the necessary additional force. All movements were accomplished in approximately the same time (the time of the triphasic pattern), and correspondingly the velocity increased for movements of greater distance. One of the normal subjects made only 'fast ramp' movements characterized by continuous agonist activity without significant antagonist participation.

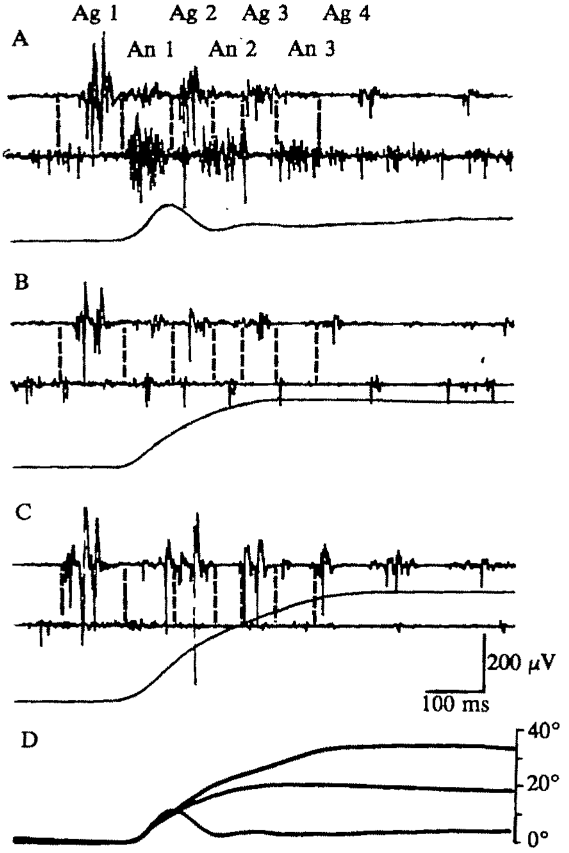

FIG. 3. Ballistic movements of a 68-year-old man with Parkinson's disease. The organization of the figure is similar to fig. 2. Note the additional cycles of bursts; the third and fourth agonist bursts are labelled Ag 3 and Ag 4 and the second and third antagonist bursts are labelled An 2 and An 3. In D, the initial part of the position traces are similar indicating similar velocities of the different movements. In A, the subject did not sustain the attempted 10-deg position, but returned quickly to near the starting point.

Seventeen of the 19 patients had at least some movements characterized by a series of alternating bursts longer than the three bursts of the triphasic pattern (figs. 3 and 4). Prolonged bursting tended to occur more often for the longer movements, and some movements required as many as five cycles (six agonist bursts alternating with five antagonist bursts).

It was our impression that multiple cycles of the triphasic pattern tended to occur more often when there was more bradykinesia, but the phenomenon was variable. If a patient made a movement requiring multiple bursts and was urged to move faster, then the next movement would often require fewer bursts. Although patients with tremor-at-rest often had multiple bursts, it was certainly not necessary for patients to have this tremor in order to show multiple bursts. Despite the bursting the movements usually were relatively smooth.

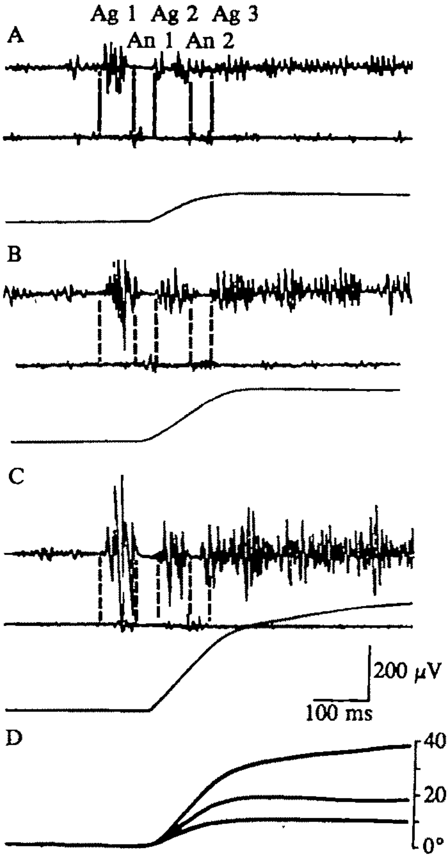

FIG. 4. Ballistic movements of a 63-year-old man with Parkinson's disease. The organization of the figure is similar to figs. 2 and 3. This person is able to increase EMG activity within the bursts to some degree, but still requires additional cycles to make longer movements.

Thirteen of the 17 patients showing a prolonged series of bursts produced at least one example of a longer movement taking more cycles of bursts than a shorter movement. In most of the examples the longer movement had about the same velocity as the shorter movement, but was continued for a longer period of time (fig. 3). It must be that the amount of EMG activity in each burst is about the same and therefore more bursts are needed to produce the force for a longer movement.

A few patients were able to increase velocity to a certain extent with longer movements, but still required extra cycles for these longer movements (fig. 4). The amount of EMG activity in each burst could be increased so that velocity could be increased, but this was not quite sufficient to complete the movement in the usual time. These patients exhibited a combination of both the normal and abnormal mechanisms. Although theoretically possible, no patient demonstrated the mechanism of increasing the frequency of bursts to make a faster and longer movement.

One of the 19 patients performed normally, not showing any examples of extra cycles. This patient was clinically assessed (before the experiment) to have only mild bradykinesia, but other patients with similar assessment did show the abnormality. The nineteenth patient showed only brief (20–40 ms) EMG bursts synchronous in the biceps and triceps which occurred at irregular intervals. Such activity might be called myoclonic and has been noted previously in patients with Parkinson's disease (Growdon, Young and Shahani, 1975).

DISCUSSION

The study of ballistic movements is a convenient window into human motor physiology. The triphasic pattern of 'agonist burst–antagonist burst–agonist burst' has been known since the early days of electromyography and has been noted repeatedly over the years for rapid movements of different joints. The normal physiology of the constancy of EMG burst lengths for movements of differing distances has been discovered only recently and has been documented for hand and forearm muscles (Freund and Büdingen, 1978; Hallett and Marsden, 1979*a*) and for animal limb movement (Ghez and Vicario, 1978). This principle of burst length constancy is here extended to elbow flexion for movements from 10 to 40 degrees. Burst durations are prolonged for patients with cerebellar lesions (Hallett, Shahani and Young, 1975*b*), patients with pyramidal tract lesions and lower motor neuron lesions (Hallett, 1979*a*), but as verified here again, burst durations remain normal in Parkinson's disease (Hallett, Shahani and Young, 1977).

It appears that the abnormal phenomenon of multiple cycles of bursts seen in some movements in patients with Parkinson's disease does explain Flowers' observations of abnormal ballistic movements. Short ballistic movements are accomplished in normal time because only the normal one cycle is required. Longer movements take longer time because more cycles are required and each cycle requires a relatively fixed amount of time. Movements of different distance are accomplished with constant velocity because the initial cycles of bursts have about the same amount of EMG activity. Thus, longer movements are made by continuing the bursting for a longer period of time. Normally the amount of EMG activity in a burst is increased for longer movements; it appears that the amount of activity is limited in Parkinson's disease and the mechanism of additional cycles is used to accomplish these longer movements.

This apparent deficit in ability to increase the amount of EMG activity in a burst gives an insight into the essence of bradykinesia and thereby into the normal role of the basal ganglia in movement. Despite the large body of data about the physiology and neurology of the basal ganglia, the normal role of these structures remains remarkably obscure. Kornhuber (1971, 1974) has proposed a theory which has attracted much attention. In his view the basal ganglia and cerebellum participate in setting up the central commands for voluntary movement. This seems true and is in accord with the currently understood anatomical connections of the motor system as summarized by Kemp and Powell (1971) and Allen and Tsukahara (1974). Kornhuber has further suggested that the cerebellum helps plan ballistic movements and the basal ganglia help plan ramp movements. The evidence for this view comes mostly from studies of deranged eye movements seen as a consequence of lesions of the cerebellum and basal ganglia. There was also apparent support for this view from studies in primates by DeLong and Strick (1974) who showed that neurons in the putamen and pallidum fired more often in relation to ramp than ballistic movements.

It is quite clear that ballistic limb movements in patients with Parkinson's disease are abnormal; the data in this paper confirm and clarify the nature of the abnormality. Moreover, the recent work of DeLong and Georgopoulos (1979) shows that neurons in the basal ganglia do not fire preferentially to slower movements. The basal ganglia must contribute to the planning of ballistic movements. The notion that the basal ganglia plan only ramp movements seems wrong.

An alternative view to that of Kornhuber which has not been as popular, but which has been held by a number of workers over many years, is that the basal ganglia 'facilitate' movement. Several early thinkers suggested that the basal ganglia supplied a motor energy (*see* De Ajuriaguerra, 1975). Schwab, who made numerous clinical observations about weakness in Parkinson's disease, showed quantitatively that repetitive movements fatigued more rapidly in patients than in normals (Schwab *et al.*, 1959; England and Schwab, 1961). Additionally, he showed that patients had difficulty in trying to perform two simultaneous voluntary motor acts (Schwab, Chafetz and Walker, 1954). Schwab summarized these facts and other clinical observations with the concept that there was a difficulty in Parkinson's disease in elaborating a motor plan (Schwab and Zieper, 1965). Joubert and Barbeau (1969), on the basis of a series of tests including repetitive tasks, reaction time measures and ability to simulate gestures, came to the conclusion that there was an inability in Parkinson's disease to elaborate a motor pattern.

Buchwald, Hull, Levine and Villablanca (1975) propose that the basal ganglia make 'response sets' and 'cognitive sets' which prepare the motor system to respond to stimuli. A response set is the facilitation of the initiation and execution of a series of movements composing a complex action. Evidence for this comes in part from the facts that electrical stimulation or ablation of one caudate nucleus leads to no simple sensory or motor deficit, but to a general inhibitory and slowing effect on the contralateral limbs. A cognitive set is the facilitation of appropriate behaviours in a particular situation. Evidence for this comes in part from the fact that electrical stimulation of the basal ganglia interferes with learning and other cognitive skills such as delayed response. Hassler's (1978) view of the function of the basal ganglia is also based in part on the results of electrical stimulation studies. Stimulation of the putamen in the cat produces mostly inhibitory effects and with some parameters of stimulation will also produce some locomotor activity and facilitation of spontaneous turning. Pallidal stimulation produces excitatory effects characterized mostly by turning to the contralateral side. Hassler concludes '. . . the function of the putamen is at the same time to focus the attention, the emotional participation and the excitability on one single event by simultaneously suppressing and fading out all other happenings and motivational objects', while 'the pallidal function is . . . directing of attention to the contralateral side'.

Denny-Brown has held the view for some time from clinical observations and animal studies that the chief symptom of basal ganglia dysfunction is akinesia (Denny-Brown, 1962, 1968). Recent behavioural analysis of monkeys with restricted lesions in parts of the basal ganglia (Denny-Brown and Yanagisawa, 1976) shows a deficiency in '. . . the preparation of the mechanism preparatory to a motor performance oriented to the environment', especially visual stimulation. These authors note physiological studies which show that caudate stimulation produces widespread inhibition and restricted excitation in thalamic and cortical neurons (Buser, 1966; Frigyesi, 1972). They conclude that '. . . the basal ganglia have all the aspects of a 'clearing house' that accumulates samples of ongoing projected activity and, on a competitive basis, can facilitate any one and suppress all others'.

A possible mechanism for the facilitation of movement is to energize specific muscles for that particular movement (Hallett, 1979*b*). The notion of energizing includes *selection*, since a muscle is selected only if it is energized, and *inhibition* of inappropriate muscles. Any movement can be fully characterized by how muscles are energized and the time order in which the energized muscles are activated. It is conceivable that these two descriptors may be two separate functions. One function, which might be referred to as 'the timing', sets up programs of properly timed and sequenced muscle activity including specification of relative amplitudes in order to produce an orchestrated pattern of flexions and extensions at several joints. The second function, 'the energizing', selects the specific set of muscles to be used for a particular performance and sets the absolute amplitude for the general level of muscle activity. The energizing process might be viewed as channelling the timing program to the specific set of muscles. That the basal ganglia might aid in this second function is anatomically and physiologically plausible since the basal ganglia take non-somatotopic input (for example, visual input) and produce somatotopic output. DeLong and Georgopoulos (1979) have shown that cells in monkey basal ganglia are related more to the fact of a particular muscle being involved in a movement than with any parameter of the movement such as amplitude or velocity.

Handwriting is a good example to illustrate how these two motor functions can be separated. The style of a person's handwriting, which can be viewed as a timing program, is the same whether channelled to finger muscles using a pencil on paper or channelled to arm muscles using chalk on a blackboard. Another example would be the ability to use (or 'energize') the non-dominant arm to perform a skilled complex motor task even if in all prior experience with this task the dominant arm had been utilized.

Virtually all the pathophysiology of disorders of the basal ganglia can be described in terms of a derangement of energizing muscles. Bradykinesia results from insufficient muscle energy; the data in this paper show that patients with Parkinson's disease cannot generate the appropriate amount of EMG activity within the set time-frame of ballistic movement burst. As shown by the example of micrographia, a defect in energizing muscle need not be accompanied by a defect in muscle timing. Lack of energy is failure to select, and thus akinesia is the extreme of bradykinesia, the failure to activate the muscle at all. Since the basal ganglia are somatotopically organized, it would be possible that one part of the body is affected while another part is less affected or even normal. This would lead to the situation, for example, where a person is able to use one limb for a skilled act, but not the other limb. Only when all the basal ganglia are damaged is the bradykinesia generalized. Even then the timing program is not gone and can be utilized in situations such as paradoxical kinesia when a sudden surge of emotional energy is able to overcome the bradykinesia.

Other symptoms of basal ganglia malfunction may be viewed as inappropriate muscle activation or failure of appropriate inhibition. In athetosis there is excessive activation of inappropriate muscles including even the antagonist muscles (Denny-Brown, 1968). The term 'overflow' might be used to describe excessive muscle activation at an appropriate time; overflow is then the physiological opposite of bradykinesia (this terminology was suggested in Hallett, Chadwick and Marsden, 1977). Involutary movements such as chorea and dystonia might be viewed as released fragments of normal phasic or tonic movements at inappropriate times.

The regulation of muscle timing may be a function, at least in part, of the cerebellum. This has in fact been the chief theory of cerebellar contribution to movement from the time of Holmes (1939) and recent physiological observations in man confirm this (Hallett *et al.*, 1975*b*; Hallett and Marsden, 1979*b*). Ballistic movements are more critically timed than ramp movements which may lead to the observation that ballistic movements are more deranged with cerebellar lesions.

Bradykinesia is the physiological consequence of a variety of lesions of the basal ganglia. Loss of the dopamine-containing neurons in the substantia nigra which leads to Parkinson's disease does result in bradykinesia as the central disorder. Bradykinesia is the symptom best related to the reduction in striatal dopamine (Bernheimer, Birkmayer, Hornykiewicz, Jellinger and Seitelberger, 1973). In animal models lesions limited to the substantia nigra produce only bradykinesia (Poirier, Filion, Langelier and Larochelle, 1975). Production of tremor and rigidity require additional lesions.

It should be noted that bradykinesia is a labile deficit varying in time depending in part on the changing amount of emotional investment in the movement. Paradoxical kinesia is the best example of this lability, but the phenomenon was apparent in this study in regard to the variable number of cycles of bursts for the same required movement in successive trials.

It is difficult to avoid commenting on the similarity of the EMG appearance of multiple bursts generated in attempting to make a movement to the bursts in tremor-at-rest seen also in patients with Parkinson's disease. Indeed, in patients with a prominent tremor-at-rest, it is difficult to say where the tremor ends and the movement begins. Previously the suggestion was made that tremor-at-rest might be considered the repetitive running of the ballistic movement pattern (Hallett, Shahani and Young, 1977). The observations here show how repetitive running of this pattern can be a compensatory mechanism for the major deficit of bradykinesia in Parkinson's disease. It is not clear at the present time, however, how the tremor-at-rest itself can be compensatory unless it enables the shaking limb to initiate movement more rapidly.

SUMMARY

Patients with Parkinson's disease were asked to make ballistic elbow flexion movements of 10, 20 and 40 degrees. Normal subjects made all these movements in the same amount of time with a single 'triphasic' EMG pattern of successive bursts in biceps, triceps and biceps. Almost all the patients made some movements requiring additional cycles of alternating biceps and triceps activity. Most of the patients exhibited at least one example of a longer movement taking more cycles than a shorter movement. It is argued that this behaviour explains previous kinematic analyses of movement in patients with Parkinson's disease and represents a physiological mechanism of bradykinesia. In part on the basis of the data presented here, it is suggested that a normal role of the basal ganglia in movement is to energize the appropriate muscles required to make the movement.

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A DISTINCT FORM OF ADULT POLYGLUCOSAN BODY DISEASE WITH MASSIVE INVOLVEMENT OF CENTRAL AND PERIPHERAL NEURONAL PROCESSES AND ASTROCYTES

A REPORT OF FOUR CASES AND A REVIEW OF THE OCCURRENCE OF POLYGLUCOSAN BODIES IN OTHER CONDITIONS SUCH AS LAFORA'S DISEASE AND NORMAL AGEING

by YVON ROBITAILLE, STIRLING CARPENTER, GEORGE KARPATI
and SALVATORE DiMAURO

(From the Departments of Neurology-Neurosurgery and Pathology, McGill University, the Montreal Neurological Institute, the Jewish General Hospital, Montreal and The Department of Neurology, College of Physicians and Surgeons of Columbia University, New York)

INTRODUCTION

THIS paper describes 4 patients who had a relatively stereotyped chronic neurological disease associated with unusual pathological findings. Salient features included progressive lower and upper motor neuron involvement, marked sensory loss predominantly in the lower extremities, neurogenic bladder and, in 2 patients, dementia. Enormous numbers of structures that resembled Lafora bodies and corpora amylacea were found both in central and peripheral neural processes and in astrocytes but not in perikarya. This prompted us to re-examine the various conditions in which similar structures have been reported. We concluded that a more general name—polyglucosan bodies—can usefully be applied to them in all the various circumstances in which they occur. Chemical analysis has shown that both Lafora bodies and corpora amylacea are made up largely of glucose polymers, that is, of polyglucosans. Our cases appear to form a distinct clinical-pathological entity, which may be diagnosable during life by sural nerve biopsy.

CASE REPORTS

Case 1

This patient died at the age of 64 years. There was no family history of neurological disease. At the age of 43 years, he was admitted to a psychiatric hospital because of incapacity to work, due to paranoid delusions. He showed an almost complete lack of emotional response and no insight. Intellect, judgement, memory and attention were rated fair. Tendon reflexes were brisk, and there were bilateral Babinski signs. Simple schizophrenia was diagnosed and he received electroconvulsive therapy. He was discharged a year later and readmitted at the age of 45 years, for similar reasons. Lower limb weakness began insidiously at this time, but it did not impede walking until the age of 53 years, when severe worsening caused admission to a general hospital. Neurological examination was as before, with added features of a widebased gait and spastic lower limbs. There was a moderate thoracic kyphoscoliosis. Myelogram and analysis of spinal fluid were normal. Cystoscopy revealed a chronic neurogenic bladder. Normal examinations included EEG, ECG, blood counts, several pre- and post-prandial blood sugars and serum cholesterol. The diagnosis on discharge was multiple sclerosis. At the age of 55 years, urinary incontinence became such a problem that he underwent a suprapubic cystostomy. An intracapsular cataract of the right eye was removed at the age of 56 years. At 58 years of age, position and vibration perception were noted to be impaired in his lower limbs. At 59 years of age, perception of pin-prick became impaired. He was found to have poor vision and wasted interossei in both hands. His mental state was that of chronic confusion with poor recent memory. The last five years of his life were spent in a hospital for the chronically disabled, where he developed a decubitus ulcer and died of pneumonia at 64 years of age.

Case 2

This patient died at the age of 67 years, after a neurological illness lasting twenty years which had been clinically considered to be multiple sclerosis. No neurological disease is known to have occurred previously in the family. During life no disorder of carbohydrate metabolism was suspected; several pre- and post-prandial blood sugar determinations were normal. The initial symptoms were progressive difficulty in walking and low back pain. On neurological examination at the age of 47 years, she showed spastic paraplegia, with brisk tendon reflexes and bilateral Babinski signs. At the age of 57 years, she showed, in addition, absent vibration perception and decreased pain sensation in both lower limbs, with a poorly defined level about T5, above which no abnormality was then found. She was orientated but vague, with poor co-operation. At the age of 64 years, poor memory and motor impersistence were noted. She then showed a slight increase of tone in the upper extremities and a wasted dorsal interosseous muscle in the right hand. One year later an ophthalmologist diagnosed optic atrophy. Her last four years were passed bedridden in a convalescent hospital. Death followed a five-day acute illness, associated with slurring of speech and marked confusion, progressing to coma.

Case 3

This 59-year-old patient was investigated for progressive difficulty in walking, which had started eight years previously. Onset was insidious. Urinary frequency developed during the same period. On examination the patient was alert and orientated. Gait was wide-based and shuffling, with difficulty lifting her legs and feet. There was subtle but definite dysmetria on finger-to-nose testing, worse on the left. Rapid alternating movements of the fingers were somewhat impaired. Muscle strength and bulk in the arms was normal, but tendon reflexes were hypoactive. Abdominal reflexes were absent. There was a severe flaccid weakness of the legs, with wasting of muscle but no fasciculations. Tendon reflexes were absent in the legs. Plantar responses were equivocal. EMG showed normal conduction velocity of the right median nerve and normal sensory evoked potentials with normal latency. Motor unit count from the right thenar group was normal. Needle electrode studies in the right deltoid, tibialis, anterior biceps, wrist extensors and left and right quadriceps muscles, showed no spontaneous activity at rest. On volitional movement there was reduced recruitment of high amplitude, long duration units. It was concluded that there was evidence of diffuse lower motor neuron disease. X-rays showed a small intrasacral meningocele at the S2 level. A myelogram showed minor degenerative disc disease at the C5-6 level. Spinal fluid protein was 61 mg per cent. A muscle and nerve biopsy was performed.

Case 4

This patient was admitted at the age of 65 years. She is the sister of Case 3. There are also 4 normal siblings in the family. Her illness began fourteen years before with insidious onset of weakness and stiffness of the legs, associated with urinary urgency and incontinence. Four years after onset, spinal fluid protein was 38 mg per cent and a myelogram was unremarkable. Eleven years after onset, even assisted walking became impossible. She also became unable to pass urine and an ileal conduit was constructed. She noted increasing difficulty using her arms. On examination she was orientated. There were bilateral cataracts. There was atrophy of intrinsic hand muscles. Rapid alternating movements were poorly performed by the hands. Upper limbs had normal tone. Tendon reflexes in the arms were normal. There was decreased power in the hands. Tendon reflexes in the legs were absent. The lower limbs showed marked flaccid weakness with only a flicker of movement remaining in the extensors of the toes on the left. Vibration perception was absent below the iliac crest. Pain and temperature perception was decreased roughly below the level of T5. Plantar responses were extensor. Electromyography showed evidence of diffuse lower motor neuron disease. A muscle and nerve biopsy was performed.

RESULTS OF INVESTIGATIONS

Gross Autopsy Findings

Case 1. The brain weighed 1200 g. There was mild arteriosclerosis of large vessels. The optic nerves and chiasm were atrophic. On section, poorly demarcated small, greyish discoloured areas were seen in the hemispheric white matter and irregular small cavities in the putamina. There was mild ventricular dilatation. The spinal cord appeared reduced to half the normal anterior-posterior diameter in all regions. Some grey discolouration was seen in the lateral columns in the lower cord. Nerve roots appeared slightly thin.

Case 2. The brain weighed 1110 g before fixation and showed mild fronto-temporo-parietal atrophy, with slight ventricular dilatation. A fresh hæmorrhage 3 × 2 × 2.5 cm was found in the right putamen. Small cavities the size of lacunar infarcts were present bilaterally in the putamina. Four small, firm, well circumscribed nodules projected into the lateral ventricles, the largest of these being 0.6 cm in diameter. Brain-stem and cerebellum were grossly unremarkable. The spinal cord was markedly atrophic, being roughly half of normal in cross-sectional area. Yellowish discolouration could be seen in the posterior columns on section, more marked in the cervical region.

Microscopic Findings

Cases 1 and 2. In all sections of brain and cord there were large numbers of sharply demarcated microscopic structures which we have identified as polyglucosan bodies. Most of them appeared spherical, but there were also elongated thread-like forms, especially in the grey matter. Some elongated ones ended in a spherical expansion. The bodies were most easily seen on the PAS-dimedone stain, which stained them all brightly, sharply and uniformly (figs. 1 and 2). Most were also stained by Alcian blue at pH 2.5. With Luxol-fast blue-cresyl violet, they were pale blue. With hæmatoxylin and eosin they showed varying degrees of basophilia. Those in the white matter were usually strongly basophilic, while those in the grey matter were usually pale or almost unstained. As a result, those in the cortex which were below 3 μm in size were undetectable with hæmatoxylin and eosin. With this stain many of the larger bodies showed layering, sometimes in the form of an interior darker circle, sometimes a lighter periphery, often a sunburnt appearance around the periphery. Some bodies had eosinophilic material on their periphery (fig. 2A) or in their centre, and some were totally eosinophilic. These tended to have an irregular mulberry-like outline and were localized particularly to areas such as the vicinity of the dentate gyrus, the deep cerebellar white matter, the middle cerebellar peduncles and the thalamus. They were also seen occasionally in the internal capsule, the spinal white matter and beneath the pia over the cortex.

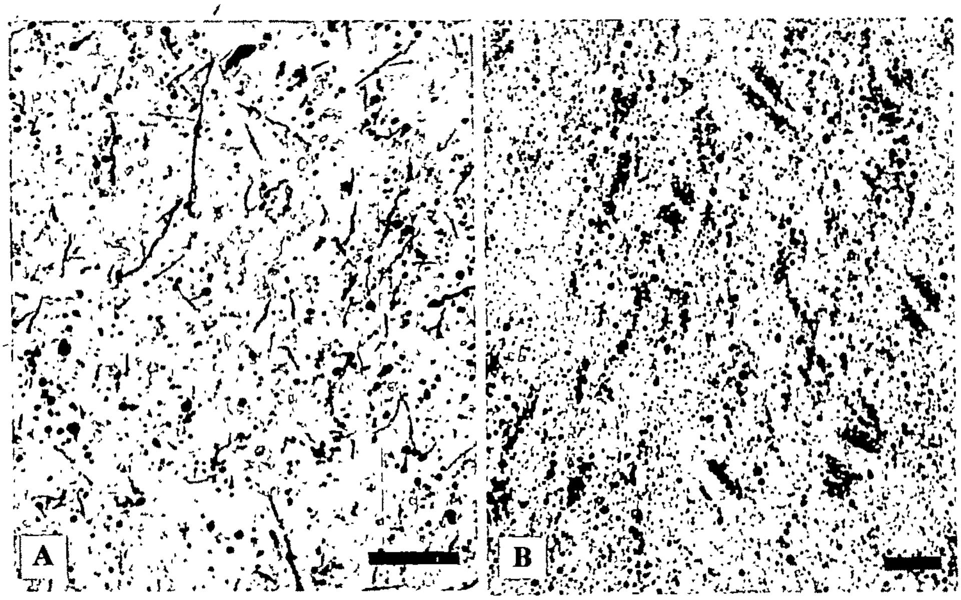

FIG. 1. *Case 1.* 20 μm thick section. PAS-dimedone hæmatoxylin. A, in the cerebral cortex numerous tiny polyglucosan bodies are present as well as many elongated ones. Bar = 50 μm. B, in the subcortical white matter the polyglucosan bodies are especially concentrated around vessels. Bar = 200 μm.

The polyglucosan bodies never appeared to be in perikarya. By light microscopy, it was usually not possible to say what type of process contained them, or even that they were not extracellular. Some were definitely intra-axonal because they were surrounded by neurofilaments with the Bodian stain, or by a myelin sheath with Luxol-fast blue. Others, particularly around vessels in the middle cerebellar peduncle, appeared to be embraced by thickened astrocytic processes. The distribution of polyglucosan bodies in the nervous system in both cases is indicated in Table 1.

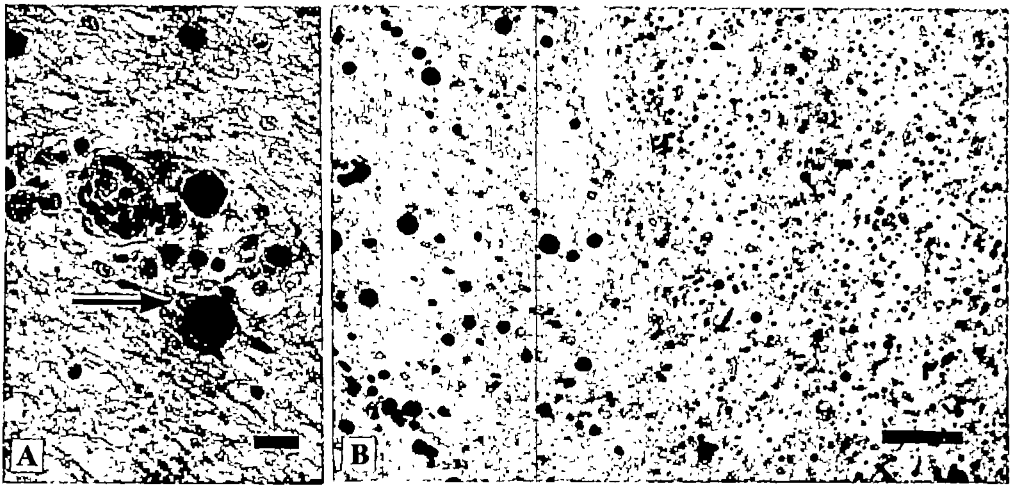

FIG. 2. *Case 1.* A, a perivascular cluster of polyglucosan bodies from the middle cerebral peduncle. One (arrow) has an irregular eosinophilic rim. Hæmatoxylin-eosin. Bar = 10 μm. B, compare the number and size of polyglucosan bodies in the caudate nucleus on the right with those in the white matter on the left; 20 μm thick section. PAS-dimedone hæmatoxylin. Bar = 50 μm.

Bodies averaging 10 μm in size were found subpially and in the molecular layer, the concentration varying from area to area, though the subpial collections tended to be heavier at the bases of sulci. In the middle four cortical layers the bodies were far more numerous, but smaller, averaging 1 to 2 μm in size. Here there were many elongated forms, some of them traceable for up to 150 μm (fig. 1A). They were often directed tangentially to the cortical surface. The fourth cortical layer was the most heavily involved, particularly in the calcarine cortex. In the cerebral white matter, while tiny (1 to 2 μm) bodies were present, there were also many larger ones up to 25 μm in size. The large ones showed some tendency to be concentrated around vessels (fig. 1B). The corpus callosum was especially heavily involved, along with the adjacent part of the corona radiata. The subependymal nodules in Case 2 were composed of well differentiated astrocytes, associated with huge numbers of polyglucosan bodies. In Case 1 there was a distinct concentration of bodies beneath the ependyma, without encroachment on the ventricle. The caudate and putamen contained extremely numerous bodies, mostly less than 5 μm in size, with both rounded and elongated forms (fig. 2B). Neither axons nor glial fibres appeared to embrace them. The thalamus contained extremely numerous bodies, most below 5 μm in size with a high proportion of elongated ones. In the hippocampus of Case 1 polyglucosan bodies were less numerous in Sommer's sector where neuronal loss was present. They were particularly numerous in both cases in the end-plate close to the dentate cells, where they were as large as the ones seen in the white matter. In the cerebellum, there was an inconstant subpial layer of medium-sized bodies. A sprinkling of small- and medium-sized ones, up to 10 μm, was seen in the molecular layer. Occasional ones were scattered in the granule cell layer, some of these being elongated. In the white matter of the folia they were variable in size and not very numerous, while by contrast, in the deep cerebellar white matter there were very many large ones which were particularly concentrated around vessels. In the immediate vicinity of the dentate cells, there were numerous small ones below 5 μm in size, some of them elongated.

TABLE 1. DISTRIBUTION OF POLYGLUCOSAN BODIES IN THE NERVOUS SYSTEM IN CASES 1 AND 2 RATED ON AN ARBITRARY SCALE OF 0 TO +4

Location	*Small* (< 5 μm)	*Large* (5 to 20 μm)	*Very large* (> 20 μm)	*Elongated*
Cortex subpial	+1	+2	0	0
Cortex 2nd to 5th layers	+2 to +4	+1	0	+1 to +2
Cortex 6th layer	+1	+2	0	0
Hemispheric white matter	+2	+3 to +4	+1	+1
Corpus callosum	+2	+4	0	+2
Striatum	+4	+1	0	+1 to +2
Thalamus	+4	+1	0	+3
Optic tract	+2	+4	+1	+3
Cerebellar cortex subpial	+1	+1	0	0
Cerebellar cortex molecular layer	+1	+1	0	0
Cerebellar cortex granular layer	+0	+2	0	0
Cerebellar foliar white matter	+2	+1	0	+1
Cerebellar deep white matter	+1	+3	0	+1
Dentate nucleus	+2	+1	0	+1
Grisea pontis	+4	+1	0	+3
Sensory nucleus of V	+2	+3	0	0
Descending tracts in basis pontis	0	+1	0	0
Gracile, cuneate and lateral cuneate nuclei	+1	+2	+3	+1
Nucleus of vagus	+3	+2	0	0
Nucleus of XII	+2	+1	0	+1
Inferior olive	+1	0	0	0
Dorsal accessory olive	+1	+3	+1	+2
Reticular formation	+2	+2	+1	+1
Medial lemniscus, medulla	0	+1	0	0
Medullary pyramids	0	+1	0	0
Spinal cord grey matter	+2	+1	+1	+1
Spinal cord, corticospinal tracts, lumbar	+1	+1	+2	0
Spinal cord, corticospinal tracts, cervical	+1	+1	0	0
Spinal cord, tractus gracilis, cervical	+2	+2	+2	0
Dorsal root ganglion	0	0	0	0

Polyglucosan bodies were extremely numerous in the pontine grey, with an especially high proportion of thread-like forms (fig. 3). The cuneate and lateral cuneate nuclei contained many relatively large bodies, as did the immediately adjacent parts of the ascending tracts ending in these nuclei. In the spinal cord both anterior and posterior horns contained moderate numbers of polyglucosan bodies, mostly below 5 μm in size. The anterior horn cells appeared normal in number and showed no evidence of axonal reaction. Myelinated fibres were rarefied in the fasciculus gracilis in the cervical cord and in the anterior and lateral corticospinal tracts in the lumbosacral cord. These regions showed a particular abundance of very large polyglucosan bodies, over 20 μm in size. Some of these were clearly within axons. Polyglucosan bodies appeared to be largely absent on the very periphery of the cord, where in normal ageing corpora amylacea tend to occur.

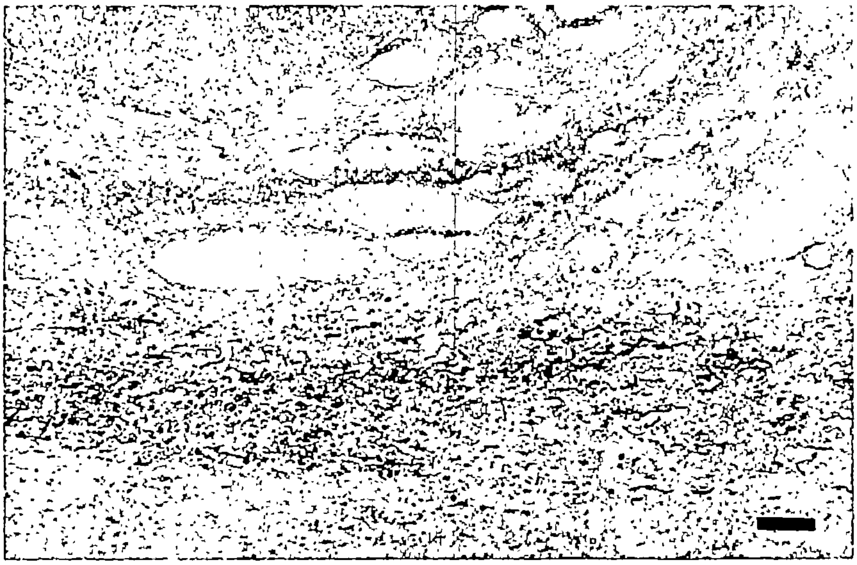

FIG. 3. *Case 1.* Note the multiple cavities in this section of the pons. Elongated polyglucosan bodies are numerous in the pontine grey. PAS-dimedone hæmatoxylin. Bar = 100 μm.

No polyglucosan bodies were seen in the anterior roots from transverse sections of cord but occasional ones were seen more distally. The dorsal root ganglion available from Case 2 was completely free. Lateral popliteal nerves from both cases showed at least one polyglucosan body per fascicle. The largest were 40 μm in size (fig. 4A). The gastrocnemius muscles from both cases showed multiple groups of angular atrophic fibres, indicating rather severe denervation atrophy. Small polyglucosan bodies were found in the intramuscular nerve twigs; many were seen inside the capsule of muscle spindles (fig. 5). There was no definite storage in the skeletal muscle.

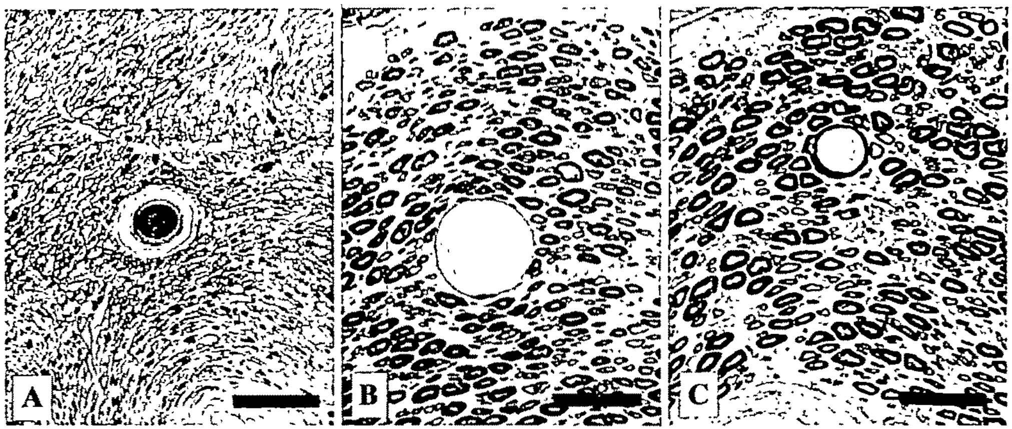

FIG. 4. A, *Case 2.* Fascicle of lateral popliteal nerve. A single huge polyglucosan body is visible. Paraffin section, hæmatoxylin-eosin. Bar = 50 μm. B, *Case 3.* Sural nerve. A huge polyglucosan body is covered by a very thin myelin sheath. The nerve otherwise appears relatively intact. Epoxy resin section, paraphenylene diamine, phase optics. Bar = 50 μm. C, *Case 4.* Sural nerve. A polyglucosan body distends a myelin sheath. The number of myelinated axons appears normal. Epoxy resin section, paraphenylene diamine, phase optics. Bar = 50 μm.

In both cases there was extensive basophilic PAS-positive accumulation within cardiac muscle fibres. In Case 1, hepatocytes, particularly in periportal regions, contained well demarcated inclusions which stained positively with PAS-dimedone and Hale's colloidal iron. Inclusions of this sort were not found in the liver of Case 2.

In addition to the presence of polyglucosan bodies, other abnormalities were found. In the hemispheric white matter of both cases there were poorly demarcated areas of myelin pallor. Axonal loss in these regions was somewhat less marked than myelin loss. Polyglucosan bodies were slightly less in number in these regions. In

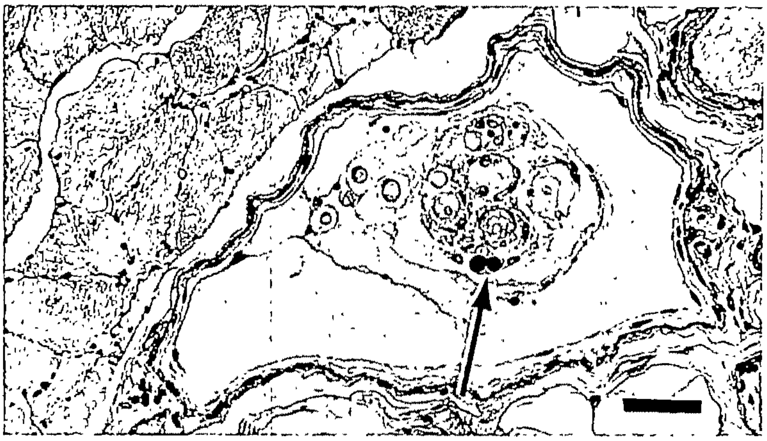

FIG. 5. *Case 2.* Two polyglucosan bodies are seen inside the capsule of a muscle spindle, probably in axons. PAS-dimedone hæmatoxylin. Bar = 50 μm.

both cases cystic lesions were present bilaterally in the globus pallidus and the posterior lateral putamen. Similar lesions were present in Case 1, medial to the dentate nucleus, and on one side of the upper part of the basis pontis (fig. 3). These cystic lesions did not contain macrophages or necrotic debris. A recent massive hæmorrhage was seen in the putamen in Case 2.

Electron Microscopy

Case 2. Portions of frontal cortex and white matter from Case 2 were post-fixed in osmium tetroxide and embedded in epoxy resin. By electron microscopy the polyglucosan bodies were formed of well preserved nonmembrane-bound, 6.5 to 7.5 nm wide, branching filaments, dotted with haphazardly distributed punctate, densely osmiophilic condensations (fig. 6). These were sometimes clumped into much larger

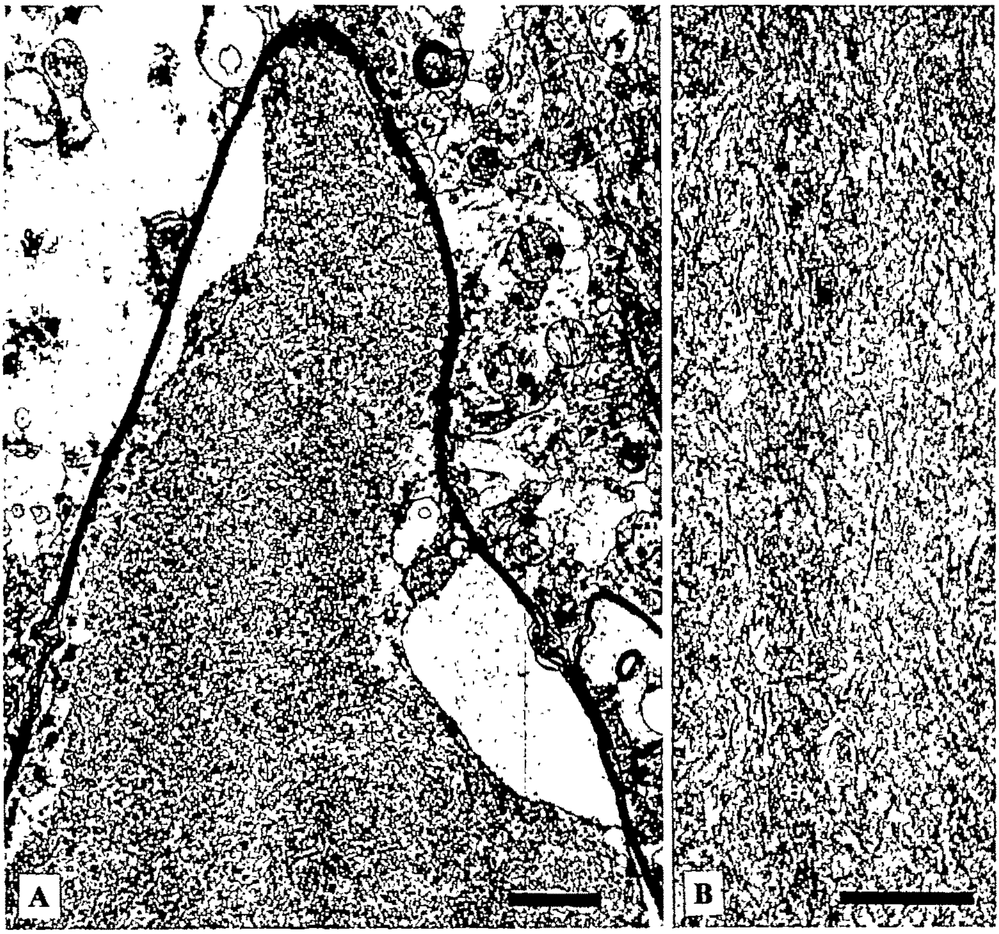

FIG. 6. *Case 2.* A, this electron micrograph shows a typical polyglucosan body surrounded by a myelin sheath. Bar = 1 μm. B, at high power the combination of filamentous and amorphous elements is seen. Bar = 0.5 μm.

dense granular structures which tended to aggregate themselves in the centre of the bodies to form rounded target-like dense areas (fig. 7). Many of the polyglucosan bodies were identified as being within axons, since they were surrounded by myelin sheaths. Such sheaths were usually much thinner than would be expected from the calibre of the axon. Glycogen particles were never observed in any close relationship with the polyglucosan bodies. No inclusions were seen within neuronal cell bodies.

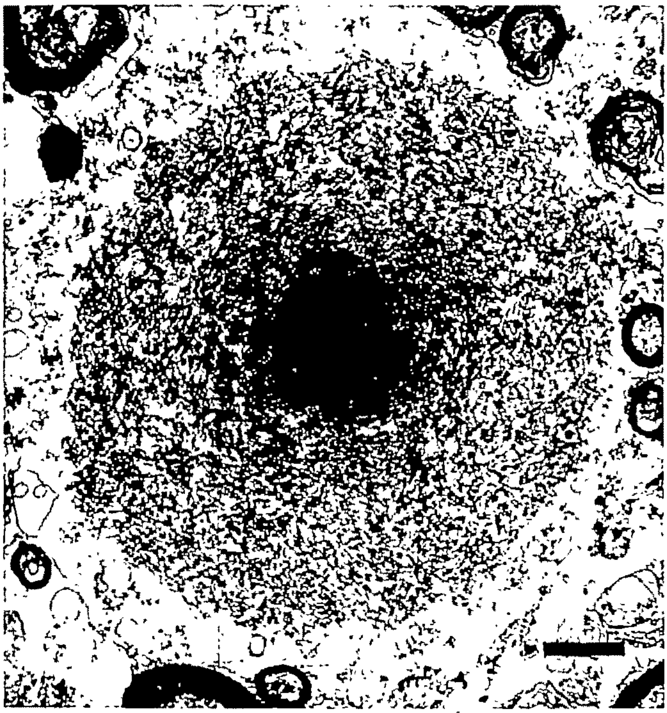

FIG. 7. *Case 2.* This electron micrograph shows a layered polyglucosan body with dense centre inside an unidentified cell process. Bar = 1 μm.

In sections taken from the hippocampal end-plates and from the cerebellar white matter, other inclusions were seen which appeared to correspond to the mulberry-shaped eosinophilic inclusions seen by light microscopy. These were characterized by clumps of filaments approximately 15 to 20 nm wide. These were sometimes interposed between typical polyglucosan bodies and the myelin sheaths around them.

Pathology

Case 3. Epoxy resin sections of the sural nerve, viewed by phase microscopy, showed apparently normal numbers of myelinated fibres. A few ovoids of Wallerian degeneration were present. Occasional axons contained amorphous material which distended them (fig. 4B). The largest such body was 50 μm in diameter. The myelin sheaths overlying such axons were thin. Cryostat sections revealed numerous rounded structures which distended axons and which were pale blue with the modified trichrome stain, basophilic with H and E, strongly positive with PAS. Alcian blue staining was variable. The bodies did not accumulate formazan with the oxidative enzyme reactions, or stain with acid phosphatase, or with diaminobenzidine peroxidase at pH6 or 9. One polyglucosan body appeared to be free in the endoneurial space but surrounded by mononuclear inflammatory cells (fig. 8A). The gastrocnemius muscle showed numerous angular atrophic fibres of both histochemical types, in between normal-sized and hypertrophic fibres. There was marked type grouping. In intramuscular nerve twigs there appeared to be a reduction in the number of myelinated axons, but no distended axons were seen. Electron microscopy on the sural nerve showed typical polyglucosan bodies.

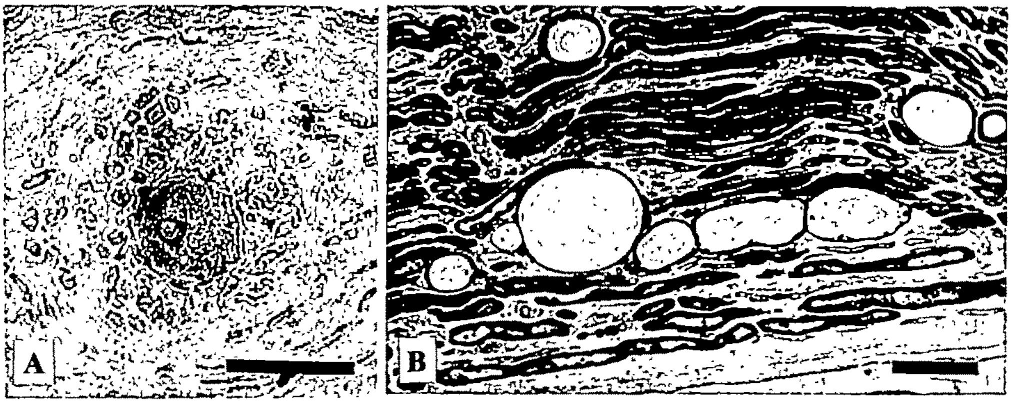

FIG. 8. A, *Case 3*. A polyglucosan body, apparently free in the endoneurium, is surrounded by mononuclear inflammatory cells. Cryostat section, Alcian blue-nuclear red. Bar = 50 μm. B, *Case 4*. In this longitudinal epoxy resin section, single axons contain more than one polyglucosan body. Paraphenylene diamine, phase optics. Bar = 50 μm.

Case 4. Epoxy resin sections of the sural nerve showed a mild decrease in the number of myelinated fibres. There were many ovoids of Wallerian degeneration. Several polyglucosan bodies were seen, the largest one of which measured 65 μm in diameter (fig. 4C). Some were elongated in shape. Some axons contained more than one such body (fig. 8B). The myelin sheaths over them were thinned. Serial sections performed on one longitudinal segment of sural nerve appeared to demonstrate the ending of an axon distal to a particularly large intra-axonal body (fig. 8B). Cryostat sections of the sural nerve show numerous foam cells of Wallerian degeneration and many axonal bodies. The gastrocnemius muscle showed that most fascicles were composed of extremely atrophic fibres and nuclear clumps. Here and there normal-sized muscle fibres were present. Many of the atrophic fibres had very high formazan content, with oxidative enzyme reactions. Polyglucosan bodies were seen in some intramuscular nerve twigs.

Electron microscopy on the sural nerve demonstrated intra-axonal polyglucosan bodies. Electron microscopy on a sample of intramuscular nerves revealed some axons which were packed with glycogen-like granules and had few or no neurofilaments within them. No polyglucosan bodies were identified in these intramuscular nerve twigs. No abnormal accumulations were seen in the skeletal muscle.

Biochemical studies

Portions of the formalin-fixed cerebrum of Case 1 were washed in distilled water overnight. The tissue was then digested at 85° C in a mixture of KOH (20 per cent) and ethanol (60 per cent). The precipitated polysaccharide was digested by acid hydrolysis; glucose was determined by a spectrophotometric assay. The polysaccharide concentration was markedly increased (1.36 mg of glucose liberated per g). A similarly fixed control brain from a patient with multi-infarct dementia gave 0.27 mg of glucose per g.

DISCUSSION

A close resemblance exists between corpora amylacea, the Lafora bodies of Lafora's disease, 'Lafora-like' bodies reported in other clinical circumstances, Bielschowsky bodies, the nervous system deposits found in some cases of type IV glycogenosis, certain intra-axonal bodies which appear to be a concomitant of normal ageing, and the microscopic bodies noted in the present cases. Electron microscopy has demonstrated that all these structures are formed of branching filaments about 8 nm in diameter, associated to some extent with granular and amorphous material (Nemetschek, Volk and Ule, 1975). By histochemistry they stain strongly with PAS-dimedone, silver proteinate, and iodine. In general they stain also with Alcian blue and Hale's colloidal iron. A rigorous histochemical differentiation between corpora amylacea and Lafora bodies does not appear possible, though in general corpora amylacea stain more strongly with most of the above reactions. The largest Lafora bodies in Lafora's disease (which are found in perikarya) have a particular tendency to be formed in two layers with a more basophilic core. Biochemical studies have shown that corpora amylacea and Lafora bodies are composed principally of glucose polymers (polyglucosans), with a small variable component of phosphate and sulphate groups, and not over 5 per cent associated protein (Yokoi, Austin, Witmer and Sakai, 1968; Sakai, Austin, Witmer and Trueb, 1969, 1970; Stam and Roukema, 1973; Yokoi, Kakayama and Negishi, 1975). The close resemblance among all these structures, and the variety of names which have been attached to them, have led us to find a common generic name for them justified and useful. Because of the biochemical evidence that they are largely made up of glucose polymers, we will use the name polyglucosan bodies.

We will review briefly the various clinical settings in which polyglucosan bodies occur, namely, (1) in Lafora's disease, (2) as a nonspecific phenomenon, generally referred to as corpora amylacea, in the ageing nervous system, (3) in a syndrome of double athetosis, (4) in a syndrome of amyotrophic lateral sclerosis, (5) in type IV glycogenosis and (6) in cases of the type reported in this paper.

(1) Lafora's disease is the best known and best studied condition which is characterized by accumulation of polyglucosan bodies. The clinical course is marked by generalized seizures, myoclonus, ataxia, dysarthria, and dementia (Lafora, 1911; Harriman and Millar, 1955; Seitelberger, Jacob, Peiffer, and Colmant, 1964; Janeway, Ravens, Pearce, Odor and Suzuki, 1967). Seizures are invariably present and myoclonus almost always. In the classical form of the disease symptoms generally began before the age of 15 years, and death occurs before the age of 25 years. A more protracted type has been described in which the onset is between 16 and 20 years of age, and death after the age of 40 years. This is sometimes called the Lundborg type. One must be careful not to confuse a separate disease which was initially reported as a variety of Lafora's disease, and which is also characterized pathologically by intraneuronal PAS-positive inclusions (Dastur, Singhal, Gootz, and Seitelberger, 1966; Bergener and Gerhard, 1970; Ota, Hisatomi, Kashiwamura, Otsu, Nakamura and Takamatsu, 1974; Dolman, 1975). No better name has yet been conferred on these inclusions than that of 'atypical myoclonus bodies'. They do not stain with iodine, with Alcian blue, or with colloidal iron; by electron microscopy they are not fibrillar. They are not polyglucosan bodies, and they shall not enter further into this discussion.

In the classical form of Lafora's disease, large polyglucosan bodies are found in the perikarya of neurons, particularly in the cerebral cortex, thalamus, globus pallidus and substantia nigra. These bodies generally show a core and periphery with somewhat different staining reactions. The staining differences have been tabulated in numerous papers (Seitelberger *et al.*, 1964; Janeway *et al.*, 1967; Dubois-Dalcq, 1969; Gambetti, DiMauro and Hirt, 1971). Not all the tables are in agreement. Considerable variation occurs in the relative proportions of core and periphery. By electron microscopy, the cores appear to be composed of granular and amorphous dense material, while the periphery is dominantly fibrillar, but the zones are not sharply demarcated (Odor, Janeway, Pearce and Ravens, 1967; Collins, Cowden and Nevis, 1968; Vanderhaeghen, 1971; Gambetti *et al.*, 1971; Schnabel and Gootz, 1971; Cajal, Blanes, Martinez, Sáenz and Gutierrez 1974). While large layered intraperikaryal polyglucosan bodies are generally emphasized as the hallmark of Lafora's disease, they are actually far outnumbered in the cerebral cortex by small homogeneous bodies lying in dust-like profusion in the neuropil of the cortex. These are virtually invisible with hæmatoxylin and eosin, but their presence is brought out by the PAS stain. The protracted or Lundborg form of Lafora's disease differs from the classical form in that perikaryal polyglucosan bodies are considerably less numerous, many polyglucosan bodies are clearly intra-axonal, and elongated forms may be seen (Jacob, 1969; Kraus-Ruppert, Ostertag and Häfner, 1970). There is a predilection for involvement of the fourth layer in the striate cortex. In all forms of Lafora's disease polyglucosan bodies have been observed in peripheral nerves, particularly intramuscular nerves. We can personally attest to their presence in the intramuscular nerves from a muscle biopsy of one patient, aged 12 years, with Lafora's disease confirmed by liver biopsy. We have not seen them, however, in two sural nerve biopsies of patients with Lafora's disease. Deposits in hepatic cells, myocardial muscle cells and skeletal muscle cells, are probably regularly present, despite much variability in their prominence (Harriman and Millar, 1955; Seitelberger *et al.*, 1964; Schwartz and Yanoff, 1965; Neville, Brooke and Austin, 1974; Coleman, Gambetti and DiMauro, 1974; Carpenter, Karpati, Andermann, Jacob and Andermann, 1974).

(2) Corpora amylacea have long been recognized as occurring routinely in the central nervous system in the course of ageing. They are seen most commonly in the subpial and subependymal regions. Their cytological localization was a matter of controversy until the electron microscopic demonstration by Ramsey (1965) that corpora amylacea in the hippocampus were clearly within astrocytic processes. The demonstration by electron microscopy of similar inclusions inside neuronal processes was first reported by Anzil, Herrlinger, Blinzinger and Kronski (1974), who studied needle samples taken immediately post-mortem from the orbital cortex of two elderly subjects known to have been free of neurological disease. Takahashi, Agari and Nakamura (1975) examined spinal cord samples from 12 patients suffering from a variety of neurological disease. In 9 of these patients they were able to demonstrate polyglucosan bodies within myelinated fibres. Those patients in which they were not found were 15 years, 34 years and 50 years of age. All but one of the patients in whom they were found were above 40 years of age.

Not only do intra-axonal and intra-astrocytic polyglucosan bodies accumulate in the central nervous system non-specifically with ageing, but they also appear in axons of intramuscular nerves. In the course of examining muscle biopsies from a large series of patients, we have occasionally encountered polyglucosan bodies in the intramuscular nerves of patients with a variety of diseases. All of them were over 40 years of age, except one patient with Lafora's disease. Therefore, in most patients over the age of 40 years we are obliged to consider the presence of occasional polyglucosan bodies in intramuscular nerves as being an incidental finding. This applies to the patient reported by Fukahara (1977) and probably to the patient reported by Yakishita, Itoh, and Nakano (1977) who had longstanding spastic paraplegia and polyglucosan bodies in intramuscular nerves. On the other hand, when the intra-axonal polyglucosan bodies appear particularly numerous and the muscle is significantly denervated, the possibility appears greater than they are pathogenetically important. In Patient 4 from this report, the polyglucosan bodies in intramuscular nerve twigs appeared relatively numerous relative to the number of myelinated axons.

In sural nerve biopsies, polyglucosan bodies occur rarely if ever as a non-specific finding. We did not even see them in the sural nerve biopsies from two patients with Lafora's disease. Therefore the polyglucosan bodies encountered in the sural nerves of our Cases 3 and 4 are highly unusual in their numbers, while their size is approached only by the similar bodies in Cases 1 and 2.

(3) Aside from the association of polyglucosan bodies with the clinically well defined phenomenon of Lafora's disease and the non-specific occurrence of polyglucosan bodies in the ageing nervous system, both within astrocytic and neuronal processes, there are several reports in which there seems to be some degree of specificity in the association of polyglucosan bodies with other neurological disease. Five patients have been reported (Bielschowsky, 1912; Vanderhaeghen, Manil, Franken and Cappel, 1967; deLeón, 1974; Ule and Volk, 1975) in whom a syndrome of longstanding double choreoathetosis was associated with striking accumulation of polyglucosan bodies in the lateral segment of the globus pallidus. Relatively few of the bodies were in perikarya. Many appeared to be in axons and to have elongated shapes. The polyglucosan bodies in this particular setting have been named Bielschowsky bodies (deLeón, 1974).

(4) A few cases of amyotrophic lateral sclerosis have been reported in which polyglucosan bodies in neuronal perikarya, resembling Lafora bodies, were present. Orthner, Becker and Müller (1973) reported two sisters with onset of disease at 38 and 39 years of age, and death after fourteen and twenty-six months, respectively. Weakness began in the arms and later involved the legs. Bulbar signs and symptoms followed. Autopsy showed marked loss of motor neurons. Lafora bodies were found in perikarya in the cortex, especially in central and precentral, and in the dentate nucleus and inferior olivary nucleus. They were also noted in the molecular layer of the cerebellum. They were not seen in the spinal cord. Other polyglucosan bodies which were called corpora amylacea, were strewn through the cortex, white matter and basal ganglia. It was felt that these could be distinguished from the Lafora bodies by their lack of a core, their more homogeneous texture and their sharp boundaries. Elongated forms are not mentioned, nor was there accumulation of polyglucosans in other organs.

Barz, Kemmer, Kunze and Sachs (1976) reported two sporadic cases of amyotrophic lateral sclerosis with onset at 39 and 43 years of age, dying after fourteen and eight months, respectively. The pathological findings, which were the same in the two cases, showed marked loss of anterior horn cells. Some of the remaining ones contained rounded PAS-negative inclusions. Layered polyglucosan bodies up to 50 μm in diameter were found in the cerebral cortex, particularly the motor cortex; some were in perikarya. They were also seen in the thalamus, globus pallidus, putamen, caudate nucleus and cerebellar cortex. Tiny dust-like polyglucosan bodies were scattered through the cortex, in the thalamus, basal ganglia and cerebellar cortex. The liver did not show definite polyglucosan storage. The myocardial cells contained abundant PAS-positive deposits. PAS-positive diastase-resistant material was seen in the extraocular muscles, but not in other skeletal muscles sampled.

Intraperikaryal polyglucosan bodies have also been reported in a few miscellaneous cases from which no consistent pattern emerges (Jacob, 1969; Yoshimura, 1977). Tiny polyglucosan bodies have been seen in Purkinje cell dendrites by electron microscopy in a case of olivo-ponto-cerebellar atrophy (Petito, Hart, Porro and Earle, 1973).

(5) In type IV glucogenosis (amylopectinosis) a recessively inherited deficiency of the branching enzyme (alpha-1,4-glucan: alpha-1,4-glucan 6-glycosyltransferase) results in an accumulation of an abnormal polysaccharide in many organs. A severe cirrhosis is present and patients die before the age of 4 years. In the central nervous system numerous small intra-astrocytic bodies have been demonstrated, which have all the histochemical and ultrastructural characteristics of polyglucosan bodies (Schochet, McCormick and Zellweger, 1970; McMaster, Powers, Hennigar, Wohltmann and Farr, 1979). Intra-axonal bodies have not, however, been demonstrated in this disease.

(6) Two published cases appear rather similar to those reported in this paper, both clinically and pathologically. Suzuki, David and Kutschman (1971) reported the case of a man dying at 62 years of age, after a three-year illness, starting with gait difficulty, followed by dementia, paraplegia, bilateral Babinski signs and later, by weakness of the arms and loss of vibration perception in the legs. Autopsy showed numerous 'Lafora-like' bodies in the brain and some in peripheral nerve. They were never seen in perikarya. Both homogeneous and laminated ones were found, as well as some eosinophilic bodies in the cerebellum. The occurrence of polyglucosan bodies in myelinated axons was confirmed by electron microscopy. Those which measured less than 10 mm in size were scattered diffusely through the central nervous system, while those 15 to 40 μm in size were more frequent in the white matter and certain deep nuclei. There was rather severe loss of anterior horn cells. Deposits roughly similar to those in the nervous system were seen in myocardium, in liver, in smooth muscle, and, to a limited extent, in skeletal muscle.

Peress, DiMauro and Roxburgh have recently (1979) published the case of a 55-year-old man dying after an eight-year illness with progressive muscle weakness, sensory loss and dementia. The pathological findings were similar to those of the case of Suzuki *et al.* (1971) with huge numbers of basophilic PAS-positive polyglucosan bodies in the brain and rare ones in the peripheral nerves. Eosinophilic neuroaxonal spheroids were noted in the substantia nigra and nucleus gracilis. Rarefaction and cavitation were found bilaterally in the cerebral and cerebellar white matter and in the medial globus pallidus. Basophilic deposits were found in myocardium, hepatocytes and smooth muscle cells. Biochemical analysis showed an increase in this brain of a amylopectin-like polysaccharide, whose iodine-polysaccharide spectrum had a higher absorbence peak than would normal glycogen.

Our cases are similar clinically and pathologically to those of Suzuki *et al.* (1971) and of Peress *et al.* (1979). Certain features we have observed in our cases deserve to be emphasized. Although there was intra-axonal accumulation of polyglucosan bodies, especially in grey matter, but also in white matter, there appeared also to be a striking accumulation in astrocytes, particularly in the cerebral and cerebellar white matter. The astrocytic localization was demonstrated partly by the striking accumulation around vessels, where astrocytic end-feet would be expected to lie, by the peculiar development of subependymal nodules, and in the demonstration by Holzer's method of glial fibrils surrounding some of the perivascular polyglucosan bodies. Intradendritic accumulation of polyglucosan bodies appeared likely in the basal ganglia.

We would also like to comment explicitly on the possibility of diagnosis of this disease in life by sural nerve biopsy. Other than in this condition, we have not seen polyglucosan bodies in sural nerve biopsies, but caution is certainly indicated until more data is available. At present we believe that the unusual size of the polyglucosan bodies seen in sural nerve axons in Cases 3 and 4 is a useful criterion in making the diagnosis. In addition, it seems desirable at present to require also a typical clinical history. The disease might also be diagnosable by liver biopsy, with appropriate PAS-dimedone and colloidal iron staining.

Little is known about factors which cause the production of polyglucosan bodies in the nervous system. The range of conditions in which they occur is puzzling. There are two clues. First there is the accumulation of apparently typical polyglucosan bodies in astrocytes (though not in neurons) in type IV glycogenosis, where deficiency of the synthetic brancher enzyme is known to occur. From the work of Peress *et al.* (1979), it appears that the accumulated polysaccharide in cases like those in this paper has considerable resemblance to amylopectin. Activity of the brancher enzyme has not been measured in this type of case; in Lafora's disease it appears to be normal (Gambetti *et al.*, 1971). A second clue is the report of polyglucosan bodies forming in axons of rats made diabetic with alloxan (Powell, Knox, Lee, Charters, Orloff, Garrett and Lampert, 1977; Powell, Ward, Garrett, Orloff and Lampert, 1979). An excess of glycogen was also seen in these axons. Nevertheless in humans no association between diabetes and polyglucosan accumulation has been noted.

A second problem concerns the intracellular site of production of the polyglucosans. While in the central nervous system numerous electron microscopic studies attest that the polyglucosan bodies are free in the cytoplasm of neurons and astrocytes, in skeletal muscle they clearly accumulate within membrane-bound spaces. These spaces are not lysosomal. From histochemical evidence it has been proposed that they are peroxisomes (Carpenter *et al.*, 1974). Powell *et al.* (1979) felt that in their diabetic rats polyglucosan bodies were formed in association with glycogen inside mitochondria and were released into the axoplasm with dissolution of the mitochondrial membranes. In Lafora's disease in the brain, small cisterns were sometimes noted around the edges of polyglucosan bodies (Collins *et al.*, 1968).

Cajal *et al.* (1974) state that when they are small, polyglucosan bodies in the brain of Lafora's disease are in fact surrounded completely by a membrane. In our cases, formation of polyglucosan bodies in the axons, as opposed to the cell bodies, appears likely.

A third problem has to do with the mechanisms of damage to the tissue in adult polyglucosan body disease. It is conceivable that there is an underlying metabolic defect which damages neurons by itself and as a side effect leads to the production of polyglucosan bodies. Aside from this speculation, the growth of a polyglucosan body in an individual axon would in time be deleterious to that axon—at the very least impeding or blocking the axonal flow. This appears especially likely when a polyglucosan body grows larger than the normal size of the axon containing it. Slippage and thinning of the myelin sheath can be observed over such axons. Small central nervous axons may well be more vulnerable in this way than large peripheral axons. Serial sections through one axon in the sural nerve biopsy of Case 3 suggested that Wallerian degeneration had occurred in the distal part of a blocked axon. Neurofilamentous increase was seen around polyglucosan bodies in many axons, especially in the anterior horns in Cases 1 and 2. The amount of damage produced to the nervous system in this way would be related to the number of axons involved and the tracts in which they occurred. Involvement proximal to branch points would presumably be more deleterious to function than involvement distally. Neuronal loss, that is, a lethal axonal reaction, was minimal in our cases, even in the anterior horns. Long ascending and descending tracts appeared to be involved distally much more than proximally.

Another aspect of tissue damage in this disease concerns the cystic lesions and rarefaction in the white matter which were seen in the case of Peress *et al.* (1979), and in our Cases 1 and 2. The cystic lesions were roughly symmetrical and involved subcortical white matter, globus pallidus, the area inferior to the putamen and the area medial to the dentate nucleus. In Case 1 there was a small cavitated lesion in the pons. The amount of atherosclerosis present in the intracranial arteries did not appear adequate to explain these lesions. One might consider three other possibilities. Excessive accumulation of polyglucosan bodies in adjacent axons might lead to sudden necrosis of many axons and release of polyglucosan bodies into the interstitial tissue, leading to inflammatory reaction and secondary tissue breakdown. Even though such an occurrence was seen in one of the sural nerve biopsies, the amount of inflammatory reaction seen did not appear to justify this possibility. One might also postulate that axons loaded with polyglucosan bodies are more prone to damage from anoxia. Finally, it seems possible that the perivascular accumulation of massive polyglucosan bodies in astrocytic end-feet might impair exchanges of essential metabolites between the parenchyma and the vessels, and thus lead to breakdown.

SUMMARY

We have described 4 patients with progressive lower and upper motor neuron deficits, marked sensory loss in the legs, 'neurogenic bladder', and, in 2 of the 4, dementia. Autopsy of two revealed a profusion of microscopic bodies resembling corpora amylacea or Lafora bodies, but restricted to processes of neurons and astrocytes. Similar (but especially large) bodies were seen within axons of sural nerves taken at biopsy from the other two patients. A general term—'polyglucosan body'—is introduced to refer to these structures in all the circumstances in which they may occur, such as in Lafora's disease, in a syndrome of longstanding double athetosis, in some cases of amyotrophic lateral sclerosis, in type IV glycogenosis, in diabetic rats, and in the normal course of ageing. Except in type IV glycogenosis, the causes for accumulation of polyglucosan bodies are unknown. They may damage tissue by more than one mechanism—probably by impeding axonal flow and impairing perivascular diffusion of metabolites.

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Address reprint requests to Dr Robitaille at Montreal Neurological Institute, 3801 University Street, Montreal, Quebec H3A 2B4, Canada.

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THE ANATOMICAL BASIS OF CONDUCTION APHASIA

by HANNA DAMASIO *and* ANTONIO R. DAMASIO

(*From the Department of Neurology (Division of Behavioral Neurology and Benton Laboratory of Neuropsychology), University of Iowa College of Medicine, Iowa City, Iowa 52242, USA*)

INTRODUCTION

THE concept of conduction aphasia has been central to the understanding of language disorders since the early writings of Wernicke (1874) and the controversy regarding its definition, anatomical basis and pathophysiological mechanism has continued to our times. But while the current definition provided by the Boston school of aphasia (Geschwind, 1965; Goodglass and Kaplan, 1972), seems to have clarified the question of the existence and clinical essence of the syndrome, Geschwind's interpretation of the disturbance as a disconnection syndrome (1965) has not been universally accepted (*see* Warrington and Shallice, 1969; Brown 1972). Such controversy often obscures the fact that the pathological substrate on which the disconnection hypothesis is based never has been challenged and appears fundamentally correct whatever stand you take on the issue of interpreting its functional significance. In this article we present anatomical findings in six cases of conduction aphasia, obtained with a method for localization of lesions in computerized tomography scans (Damasio and Damasio, 1979; Damasio, Damasio, Hamsher and Varney, 1979). We reconsider the anatomical correlates of conduction aphasia and discuss their bearing on the production of the syndrome.

METHOD

Neuropsychological Assessment

Patients were given the MAE (Multilingual Aphasia Battery; Benton, 1969; 1976) which consists of a series of standardized and validated tests (for example, Visual Naming, Sentence Repetition, Aural Comprehension, Reading Comprehension, Token Test). The diagnosis of conduction aphasia was made on the basis of results obtained in those tests but according to the Boston Diagnostic Classification of the Aphasias (Goodglass and Kaplan, 1972). The operational definition of conduction aphasia was: an aphasic syndrome with fluent, meaningful speech (in which phonemic paraphasias predominate over global ones), profound verbal repetition defect (with either entire blocking of repetition or repetition with phonemic paraphasias), partial or complete preservation or repetition of words which stand for digits, and preserved or minimally impaired aural comprehension defect. Additional neuropsychological evaluation was carried out with standardized tests of the Benton Laboratory of Neuropsychology.

Anatomical Study

Computerized tomography was performed by EMI scanners (Mark III or Whole Body Scanner). The anatomical study was conducted on the basis of CT scan films of consecutive parallel cuts with a depth of 0.8 cm..

Templates of the cuts as described previously (Damasio and Damasio, 1979; Damasio *et al.*, 1979), were prepared on the basis of brain sections and of available atlases of computerized tomography and of neuroanatomy. In the standard template of each consecutive level, cortical and subcortical areas of special interest in terms of higher nervous function were indicated by the numbers of Brodmann's map or by appropriate initials. By means of identifiable anatomical landmarks, lesions were plotted on the best fitting template and the results of the record read as a three-dimensional reconstruction.

SUBJECTS

Six patients with conduction aphasia due to stroke were selected. Only patients who could be evaluated within three months of the onset of aphasia and who were native English speakers were included in the study. All patients had right-handed ancestry and all but one were right-handed. Age range was 35 to 55 years and educational level varied between 10 and 16 years. Pertinent details of each case are summarized below.

Case 1

The patient is a 43-year-old man, right-handed, college graduate and owner/manager of a factory. In December 1978, he suffered a thrombotic stroke which produced aphasia, right central facial paralysis and right brachial paralysis. The facial and brachial weakness improved remarkably over the ensuing weeks but aphasia persisted. Speech was fluent and entirely meaningful but with occasional phonemic paraphasias generally recognized as errors by the subject. Repetition of digits was normal (Forward Digit Span = 7) but repetition of verbal material was severely impaired with phonemic paraphasias and omission of phonetic and lexical components (in the MAE Sentence Repetition Test he was unable to repeat a single sentence correctly, e.g. nil percentile). Word finding ability was defective, though less so than repetition (the patient scored in the 18th percentile in the MAE Visual Naming Test, which was low normal for his age and education). Aural comprehension was normal for simple conversational items but impaired for syntactically organized material. In the MAE Test for Aural Comprehension of Words and Phrases he scored in the 20th percentile, low normal for his age and education. The Token Test was defective (he scored 27/44). Reading comprehension was mostly normal (59th percentile in the MAE Test of Reading Comprehension of Words and Phrases) but reading aloud was marred by phonemic paraphasias. Recall of recent and remote events was excellent as were calculations and visuospatial abilities. Dichotic word listening revealed a complete extinction of the right channel.

Case 2

The patient is a 45-year-old woman, right-handed, a housewife with a ten-year education. In March 1978, she suffered a thrombotic stroke which produced an aphasia, right central facial paralysis and right brachial paralysis. Speech was fluent and meaningful. The major disturbance was in repetition of words and sentences, particularly the latter, with frequent blocking and phonemic paraphasias (in the MAE Sentence Repetition Test she was profoundly defective, e.g. nil percentile). Repetition of digits was normal (Forward Digit Span = 7). Word finding ability was within normal range (in the MAE Visual Naming Test she scored in 75 per cent percentile) as was aural comprehension for syntactically complex items but not for simple conversational items (in the MAE Test for Aural Comprehension of Words and Phrases she scored in the 20th percentile). The Token Test was defective (34/44). Reading comprehension was normal but reading aloud elicited numerous literal paraphasias. Memory was excellent in all spheres. Constructional praxis and calculation were normal. Dichotic word listening revealed a complete extinction of the right channel.

Case 3

The patient is a 47-year-old man, left-handed but with a dextral family background, a high school graduate. In November 1976, he suffered a thrombotic stroke and as a result had aphasia and right-sided paralysis of the face and upper extremity. The latter cleared while aphasia persisted. The patient was always fully orientated and with fluent meaningful speech, his major difficulty being verbal repetition of words and sentences but not of digits (in the MAE Sentence Repetition Test the patient repeated none but the simplest phrase, a score of 1, below the 2nd percentile; he could repeat five digits forward). Aural and reading comprehension were impaired for complex material but preserved otherwise. (In both the MAE Test for Aural Comprehension of Words and Phrases and the MAE Test for Reading Comprehension of words and phrases he scored in the 75th percentile). The Token Test was defective (he scored 32/44). Written calculation and visuospatial abilities were preserved.

Case 4

The patient is a 35-year-old woman, right-handed, college graduate. In April 1979, she suffered a thrombotic stroke which produced aphasia, right central facial paralysis and right brachial paralysis. Spontaneous and conversational speech was fluent and meaningful but with frequent phonemic paraphasias and occasional global paraphasias. Repetition of words and sentences was severely impaired with profuse phonemic paraphasias. Often repetition was entirely blocked and when attempted, phonetic and lexical components were omitted. At the time of admission her score in the MAE Sentence Repetition Test was 0 but then improved to 1 and 2 (three word sentences). Her Digit Span Forward initially was 6 and then improved to 7. Aural and reading comprehension were normal (in both the Aural and Reading Comprehension Tests of the MAE, the patient performed in the 65th percentile) but reading aloud was disturbed by phonemic paraphasias and omission of lexical elements. The Token Test was mildly defective (she scored 40/44). Calculation, constructional ability and general memory functions were normal.

Case 5

The patient is a 46-year-old woman, right-handed. In October 1976, she suffered a hæmorrhagic stroke. At the time she had a ten-year history of untreated systemic hypertension. After an initial period of diminished alertness and confusion she was noted to have a fluent aphasia with severely impaired verbal repetition for words and sentences but not for digits. Paraphasias were mostly phonemic but some were verbal as well and occurred frequently. Aural and reading comprehension were impaired although she was able to understand the less complex stimuli. As spontaneous speech and comprehension improved the pronounced repetition defect stood out more clearly. Her score in the MAE Sentence Repetition Test was 0. Her Digit Span Forward was 4.

Case 6

The patient is a 55-year-old woman, right-handed, a secretary. In August 1979, she suffered a stroke which manifested itself by sudden onset of difficulty in finding words and a mild paresis of the right arm and right side of the face. Her difficulty in word finding cleared and at the time of admission, other than for occasional phonemic paraphasias, her speech had normal content, articulation and rate. But her repetition, other than for digits, was severely impaired (MAE Sentence Repetition Test in nil percentile; Digit Span = 6). Aural and reading comprehension were intact (in both the Aural and Reading Comprehension Tests of the MAE she scored in the 65th percentile). Calculation, constructional ability and general memory function were normal.

In sum, these 6 patients best fit the diagnosis of conduction aphasia, given the fluency and meaningfulness of their speech, the marked defect in verbal repetition, and the comparatively preserved aural comprehension which allowed them to grasp the meaning of sentences which they could not repeat. The scores obtained in the MAE validate the clinical impression.

ANATOMICAL STUDY

Case 1

The CT scan shows an area of decreased density encompassing four consecutive cuts. Plotting of this area on the corresponding templates suggests that it involves the insular cortex and some white matter directly subjacent to it (fig. 1). The lesion extends laterally and posteriorly to involve structures of the temporal lobe particularly in the supratemporal plane, namely, part of cortical areas 22, 41 and 42, as well as white matter directly underlying them. Although the lesion does not damage the parietal lobe extensively it involves the cortex of the parietal operculum lying over the supratemporal plane (areas 3, 1, 2 and 40) as well as its corresponding white matter.

Case 2

The CT scan shows an area of decreased density which encompasses six consecutive cuts. Plotting of this area suggests that it involves the insula in most of its extent compromising its cortex and underlying white matter. It extends into the temporal lobe (areas 22, 41 and 42 and subjacent white matter) and also involves parietal cortex (area 40 and subjacent white matter). (*See* fig. 2).

Case 3

The CT scan shows an area of decreased density which encompasses four consecutive cuts. The area involves the insula in most of its extent, cortically and subcortically, and extends into the temporal lobe compromising a portion of area 22, 41 and 42 and subjacent white matter. It extends also into area 40 and corresponding white matter (fig. 3).

Case 4

The CT scan shows an area of decreased density located in approximately the same region involved in the three previous cases (fig. 4). A significant difference regards the amount of involvement of the insular region, in this case limited to its posterior portion. The involvement of the auditory complex is similar to the other cases as is the compromise of the supramarginal gyrus which is quite pronounced.

Case 5

The CT scan shows an area of increased density located deep in the basal ganglion region of the left hemisphere and encompassing three consecutive cuts. This area corresponds to the lenticular nucleus, mainly the putamen, and involves white matter underlying the insula and possibly its cortex as well as that of areas 41 and 42. Areas 22 and 40 do not appear to be directly involved but are in all likelihood displaced due to the space-occupying nature of the lesion while their white matter is undercut by the lesion (fig. 5).

Case 6

The CT scan shows areas of decreased density in the insular region, the temporal lobe (areas 22, 41 and 42 and subjacent white matter) and also in the parietal cortex (area 40 and subjacent white matter) (fig. 6).

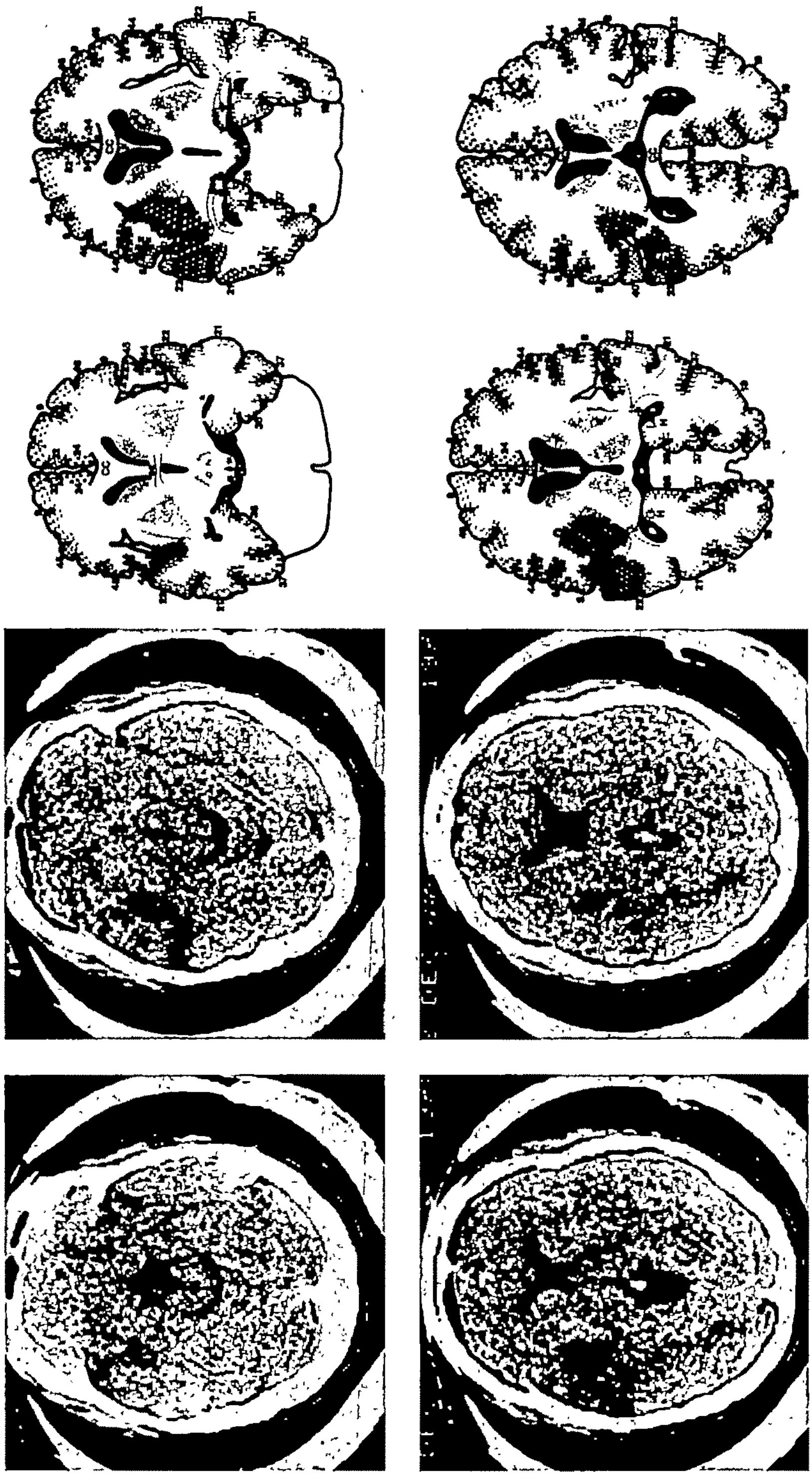

FIG. 1. CT scan and templates of *Case 1*. Note involvement of the left insula, auditory areas and supramarginal gyrus.

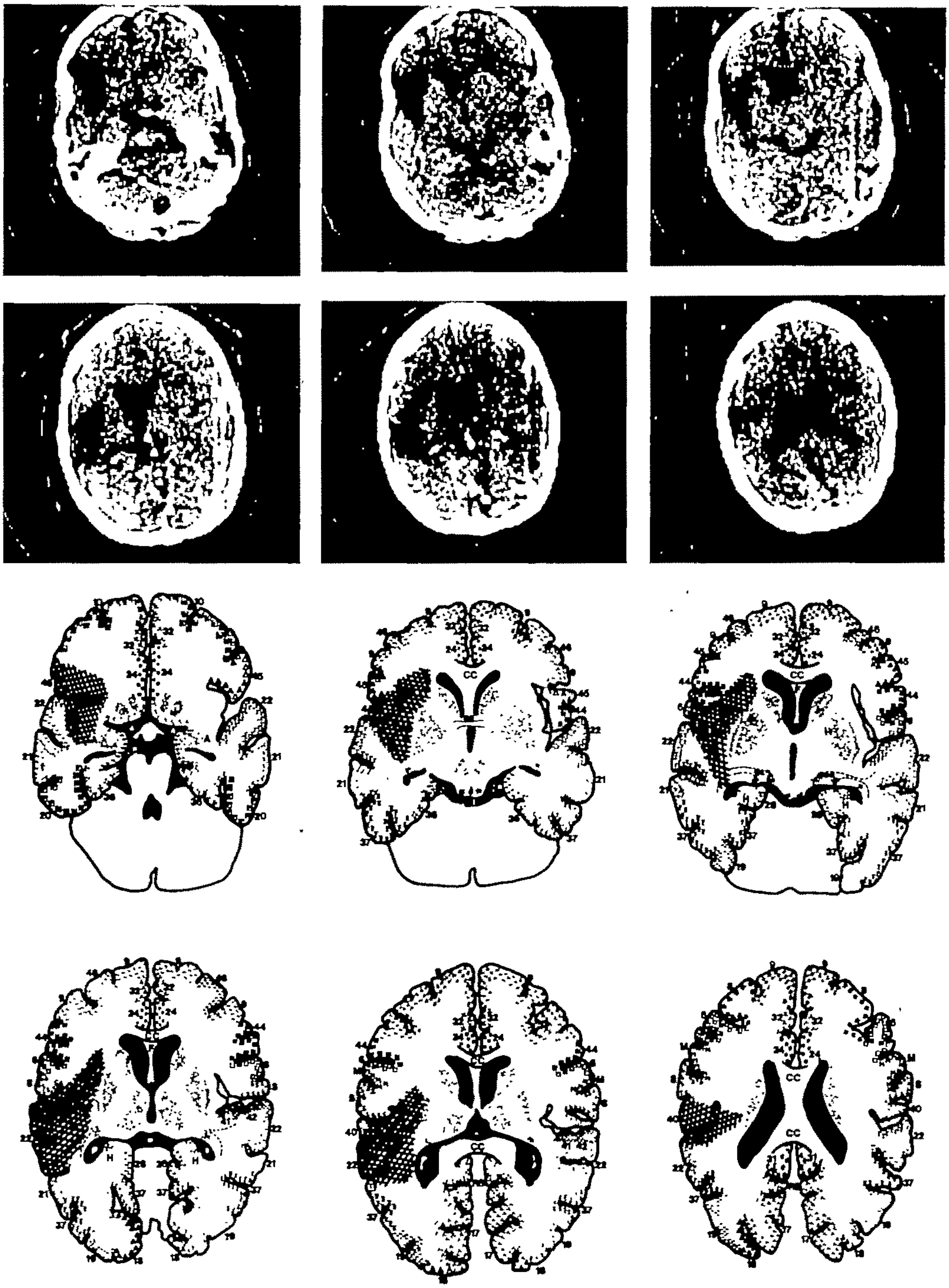

FIG. 2. CT scan and templates of *Case 2*. Note the similarity with the lesions in *Cases 1* and *3*.

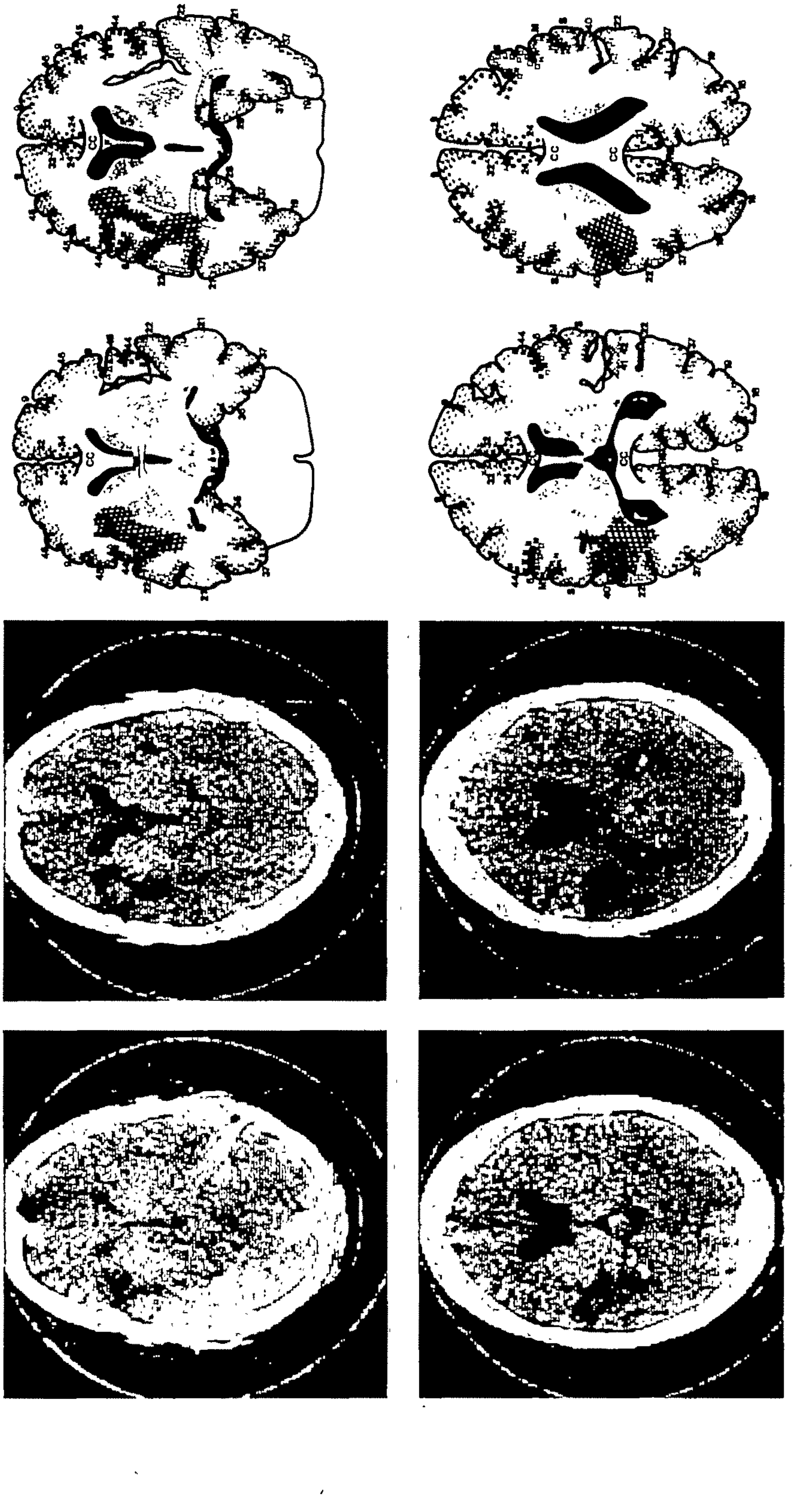

FIG. 3. CT scan and templates of *Case 3.*

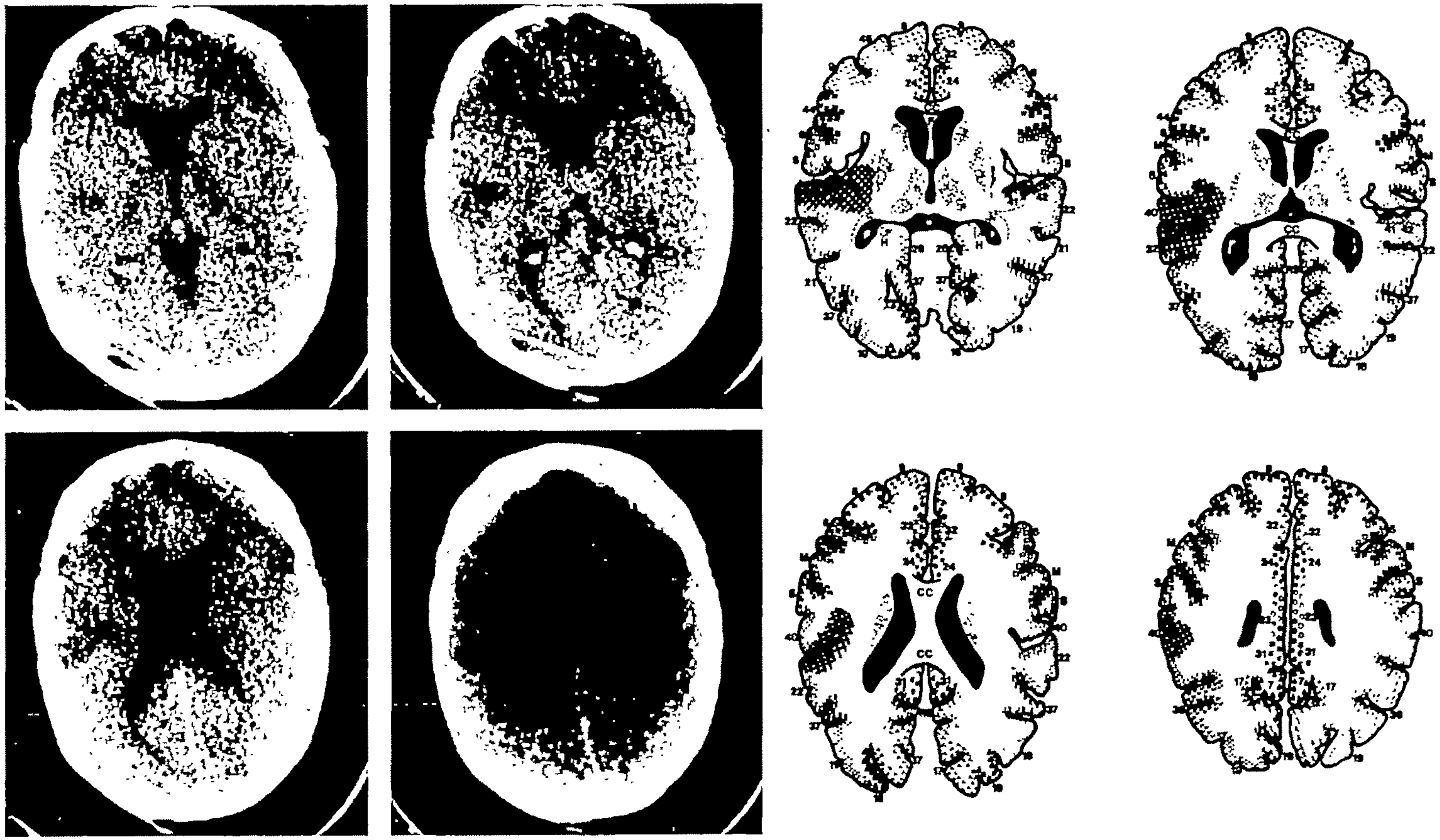

FIG. 4. CT scan and templates of *Case 4*. In comparison with previous cases, involvement of the insula is less pronounced. Distribution of lesions is otherwise comparable.

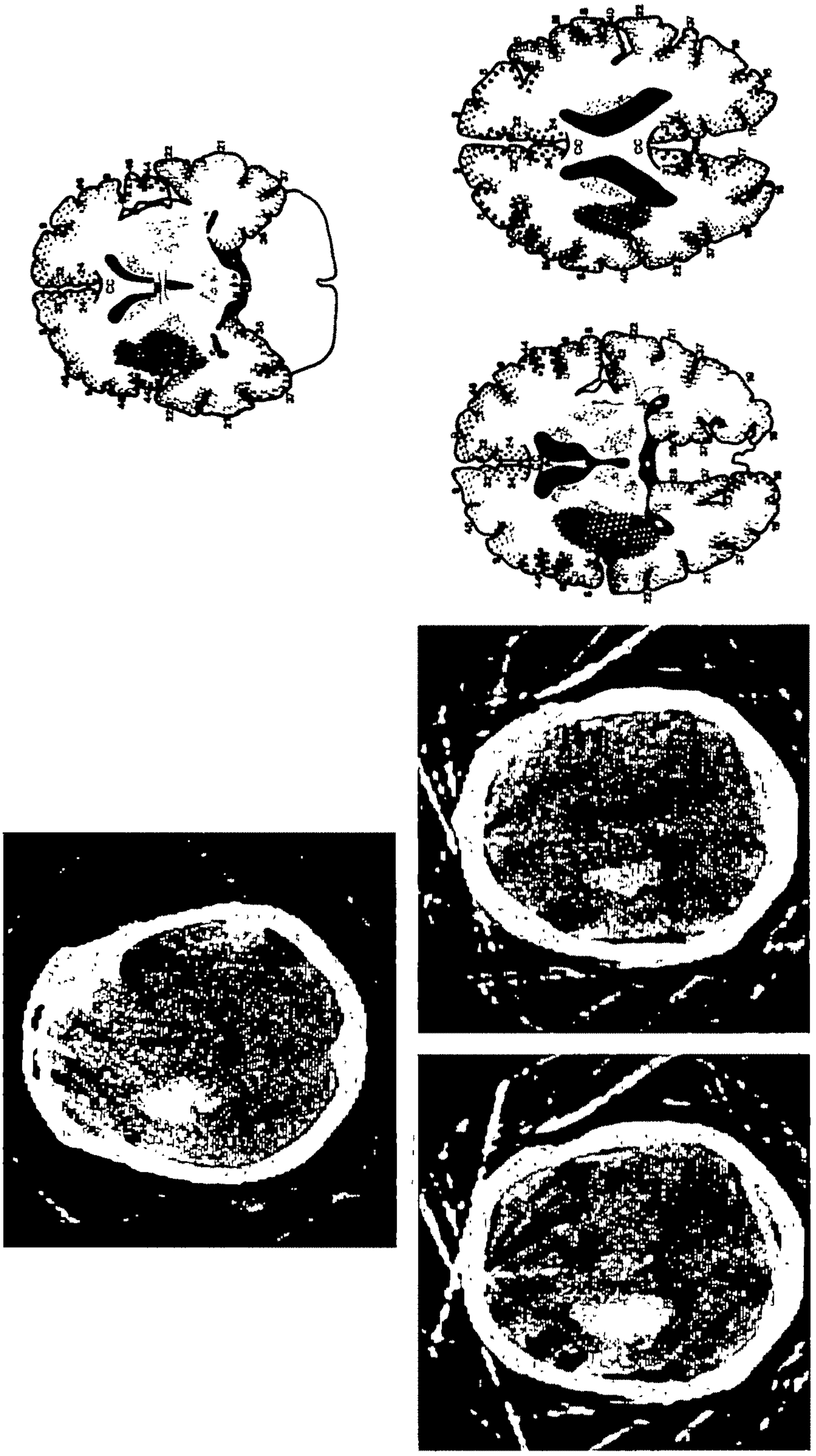

FIG. 5. CT scan and templates of *Case 5*. The area of increased density corresponds to white matter underlying insular, auditory and supramarginal cortex.

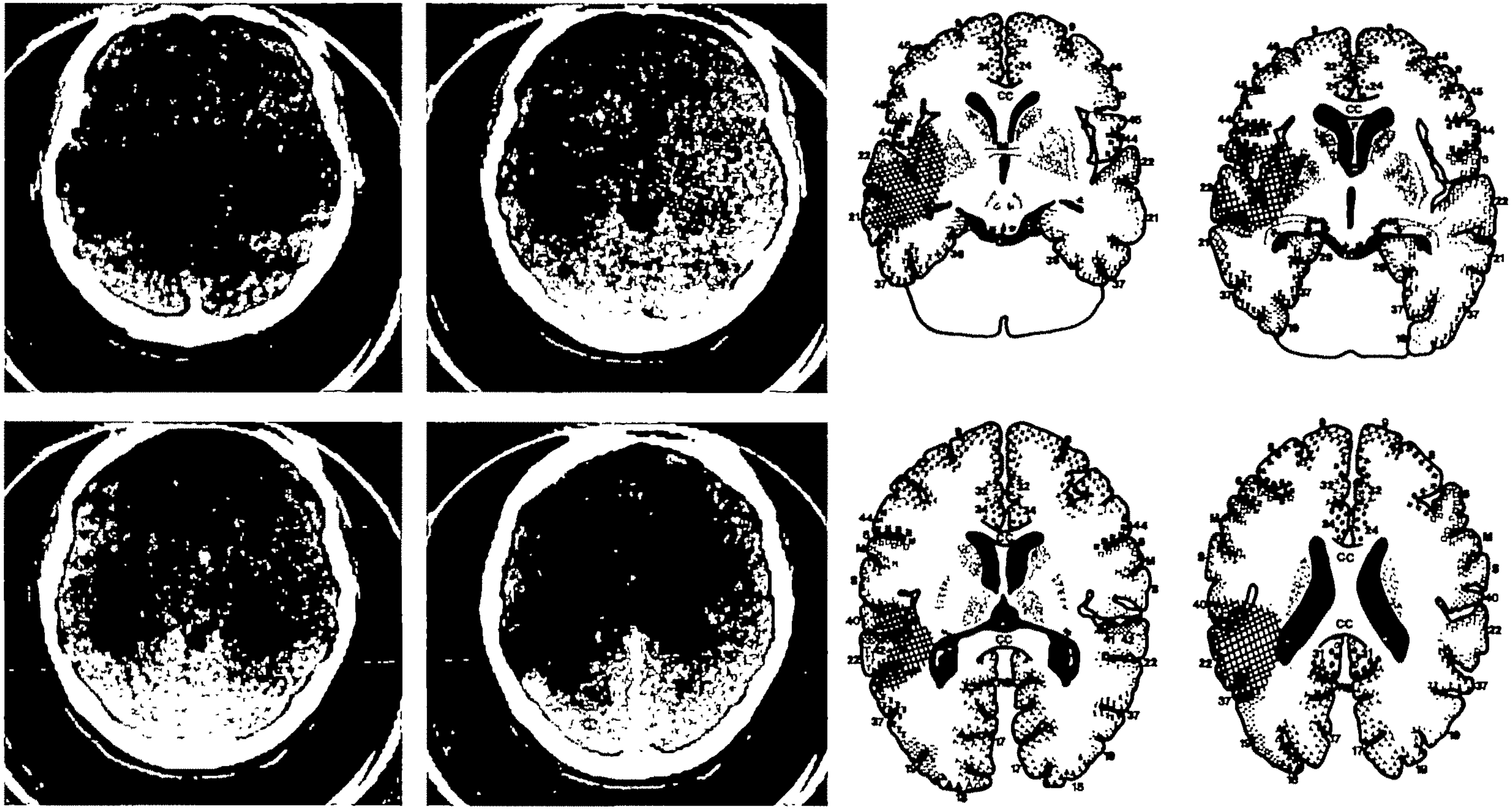

FIG. 6. CT scan and templates of *Case 6*. The areas of decreased density are placed in the region of the left insula, auditory areas and supramarginal gyrus.

In summary, 5 cases show compromise of the insular region, and 5 cases show variable degree of involvement of the superior temporal gyrus and an extension of the lesion into the inferior parietal region. In all cases the lesion is deep and compromises the white matter corresponding to the aforementioned regions. In no case is there involvement of the angular gyrus (area 39), or of the posterior portion of the second and third temporal gyri (area 37) or of Broca's area (areas 44 and 45). These neuroradiological findings are consonant with those reported by Kertesz, Harlock and Coates (1979).

DISCUSSION

Consideration of the above findings supports the notion that conduction aphasia is associated with a highly distinctive structural pattern, and that damage to the arcuate fasciculus is strongly associated with the syndrome. As defined in classical terms, that pathway originates in the cortex of the supratemporal plane, arches around the back end of the sylvian fissure and courses in the superior longitudinal fasciculus over the extreme capsule and insula, to reach the lower frontal region. There is little doubt that, in one way or another, at its origin or while coursing in the parietal operculum, the pathway is damaged in our cases. But our data also show that with the exception of Case 5, damage was not confined to the arcuate fasciculus as it involved the left auditory complex, the left insular region and the supramarginal gyrus also.

These findings merit special attention. Let us consider the ones related to the auditory complex first. The lesion In Wernicke's area was not as extensive or posteriorly placed as that seen in our cases of Wernicke's aphasia in which the posterior portion of the supratemporal plane, the parietal component of area 22 (as defined by Galaburda, Sanides and Geschwind, 1978) and part of areas 39 and 37 are always involved (Damasio *et al.*, 1979). On the other hand, a part of areas 41 and 42 appeared consistently compromised in the conduction cases, and that seems to be an inconstant feature of Wernicke's aphasia (Damasio *et al.*, 1979). The finding of involvement of the auditory complex is in line with the majority of pathological reports in the literature. Its replication suggests that conduction aphasia should probably be defined, in anatomical terms, by the pattern of intactness or damage of certain portions of the left auditory complex as much as by damage to the left arcuate fasciculus. In fact, since damage to both auditory complex and arcuate fasciculus is shared by other aphasias (for example, Wernicke's, Broca's) it is the specific pattern of compromise to either structure that renders conduction aphasia distinctive, anatomically and behaviourally.

The finding of damage to the insula is thought-provoking. In recent years damage to this region has not been considered a pertinent component of the anatomical basis of conduction aphasia. For instance, in a report on conduction aphasia (Sheremata, Andrews and Pandya, 1974) a lesion in the insula, extreme capsule, claustrum and external capsule was noted but the syndrome was interpreted as resulting from another lesion which damaged the more superiorly placed rostral arcuate fasciculus. In their review of the anatomical findings in conduction aphasia, Benson, Sheremata, Bouchard, Segerra, Price and Geschwind (1973) emphasized the importance of damage to three main structures: (1) Wernicke's area, a lesion of which was present in their Case 2 and in almost all of the few cases previously recorded; (2) the supramarginal gyrus, damaged in their Cases 1 and 3; and (3) the arcuate fasciculus, damaged deep underneath the supramarginal gyrus as could be inferred from the distribution and amount of white matter destruction in Cases 1 and 3. On discussing possible mechanisms for the genesis of conduction aphasia they suggested that two mutually exclusive anatomical patterns appear capable of producing the syndrome: (a) the supramarginal gyrus/arcuate fasciculus lesion, and (b) the auditory region lesion. They did not comment on the role of damage to the insula which was involved in their Case 2. By comparison our cases best resemble their Case 2 but with elements of Cases 1 and 2, suggesting that a combination of the two basic anatomical patterns proposed by Benson *et al.* (1973), coupled with damage to the insula also occurs in association with the syndrome. Such a combination was also present in the well documented cases of Goldstein (1911; 1948) and of Kleist (1962) and in the case of Voisin (1912).

The exact functional significance of damage to the insula may not be easy to settle. Wernicke initially predicted that the insula would be the locus for the 'sensorimotor' disconnection underlying conduction aphasia (1874) and the case of Lichtheim (1885) supported that view. But by 1908 he felt the insula was not crucial and the case of Liepmann and Pappenheim (1914), a conduction aphasia in which the insula was spared, now supported his new opinion (he maintained, however, that the syndrome resulted from disconnection although, by then, following Von Monakow, he had turned to the arcuate fasciculus as the responsible 'disconnecting' structure). Goldstein, on the other hand, again related the insula to conduction aphasia ('central aphasia' in his nomenclature) though he rejected the disconnective interpretation proposed by Wernicke. It could be argued that the finding is incidental, an addition to the more crucial damage in the arcuate fasciculus and auditory cortex. We suspect, however, that damage to the insula and to its underlying matter can be a pertinent factor in the production of the syndrome. More than the insular cortex itself, the decisive pathological element must be the destruction of white matter in the extreme capsule which, most certainly, contains vital cortico-cortical connections linking temporo-parietal structures with frontal pre-motor structures. D. N. Pandya (1979) has demonstrated that connections from auditory cortex to the pre-motor frontal lobe travel in the extreme capsule, underneath the insular cortex. Such a course is in fact quite logical although classic anatomical texts always portray those connections as part of the superior longitudinal fasciculus, travelling above the extreme capsule and insular cortex. The latter concept is derived from dissection anatomy and appears incorrect, being accurate only in regard to connections of the most posterior aspect of the auditory association cortex but not in relation to the remainder of the auditory complex. In sum, it appears that damage to a specific set of temporo-parietal connections, be it in the parietal operculum or underneath the insula, can be associated with impaired repetition, just as the relative intactness of Wernicke's area can be associated with considerable sparing of aural comprehension.

Anatomical data may help resolve the issue of behavioural interpretation. The variety of structures potentially involved makes it necessary to cast doubts on explanations based on a single disruptive factor (for example, mnestic defect). The act of immediate oral repetition of a heard sentence presupposes a variety of operations: phonological identification, immediate memory for phonemes and for their sequence, and open access to an intact sensorimotor effector. In all likelihood, those steps depend on function of the left auditory cortex and of its connections to lower parietal and frontal cortex and possibly to the basal ganglia also. As we have just seen, the anatomical patterns associated with conduction aphasia are such that in any given instance more than one functional defect may be at play, for instance, impairment in immediate memory for phonemes combined with impaired access to a sensorimotor effector.

The issue of whether abnormal repetition with phonemic paraphasias is the result of left or right hemisphere function (raised by Liepmann and Pappenheim (1914)) and discussed by Goldstein (1948), Kleist (1962), and Kinsbourne (1971), can not be satisfactorily resolved by anatomical data. But the remarkable preservation of a considerable portion of left speech area seen in most cases would probably support the contention that whatever abnormal linguistic production is available can be the result of residual left hemisphere function, even if auditory information would have to arrive in the right auditory cortex first and from there be transferred to left auditory association cortex. Finally, the present anatomical evidence supports, in good measure, both Wernicke's original prediction and Geschwind's now classical anatomical account of the syndrome.

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EFFECTS OF AGEING ON LOCAL RATES OF CEREBRAL GLUCOSE UTILIZATION IN THE RAT[1]

by C. B. SMITH, C. GOOCHEE, S. I. RAPOPORT *and* L. SOKOLOFF

(From the Laboratory of Cerebral Metabolism, National Institute of Mental Health, United States Public Health Service, Department of Health, Education and Welfare, Bethesda, Maryland 20205 and Laboratory of Neuroscience, National Institute on Aging, United States Public Health Service, Department of Health, Education and Welfare, Baltimore, Maryland 21224, USA)

INTRODUCTION

AGEING is associated with a generalized diminution in cerebral functional capacity. Although changes in cerebral functions are exacerbated by the presence of disease, they are evident even in elderly subjects carefully selected for relative freedom from disease (Birren, Butler, Greenhouse, Sokoloff and Yarrow, 1963). Ageing in such subjects is accompanied by a general slowing of reaction times, particularly those associated with complex behavioural patterns (reviewed by Birren, Woods and Williams, 1979). Levels of performance on tests of psychomotor functions and nonverbal intelligence are reduced (Botwinick and Birren, 1963; Birren, Botwinick, Weiss and Morrison, 1963; Granick and Patterson, 1971). Cerebral blood flow and oxygen consumption remain normal in normal elderly subjects (Dastur, Lane, Hansen, Kety, Butler, Perlin and Sokoloff, 1963), but cerebral glucose consumption is reduced (Dastur *et al.*, 1963), possibly due to increased blood levels of ketone bodies and their utilization in place of glucose by the brain (Gottstein, Held, Müller and Berghoff, 1970; Sokoloff, 1975). The frequency of the dominant alpha rhythm of the resting electroencephalogram is somewhat slowed (Obrist, 1963), and stage 4 and REM sleep are reduced in duration (Feinberg, Koresko and Heller, 1967). Histological examination of brains from normal aged individuals reveals a number of degenerative changes, that is, losses of neurons (Brody, 1955, 1970; Colon, 1972; Hall, Miller and Corsellis, 1975), dendrites and dendritic spines (Scheibel, Lindsay, Tomiyasu and Scheibel, 1975, 1976); these changes have a predilection for certain brain regions. In view of the non-uniform distribution of the pathological changes and the specificity of some of the losses in performance, age-related changes in the functioning of the central nervous system might also be expected to exhibit regional selectivity.

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[1] A preliminary report of portions of this work was presented at the Tenth Annual Meeting of the American Society for Neurochemistry, Charleston, South Carolina, March 1979 (Smith, Fredericks, Rapoport and Sokoloff, 1979).

The present studies were carried out in normal albino rats. Normal ageing in the rat is also accompanied by behavioural modifications as well as histopathological changes in the brain (Feldman, 1976; Geinisman, Bondareff and Dodge, 1978; Ordy, Brizzee, Kaack and Hansche, 1978; Vaughan, 1977). The rat has the distinct advantage of being relatively free of atherosclerosis (Fox, 1933), which eliminates the confounding secondary effects of vascular pathology.

In these studies we have applied the deoxyglucose method (Sokoloff, Reivich, Kennedy, Des Rosiers, Patlak, Pettigrew, Sakurada and Shinohara, 1977) to investigate the effects of ageing on local cerebral glucose utilization. Inasmuch as local glucose utilization has been found to be closely coupled with local functional activity (Sokoloff, 1977), the purpose of these studies was not only to examine the distribution of the changes in local cerebral energy metabolism but also to identify specific regions in the brain with altered functional activity in association with ageing.

METHODS

Animals

Normal male Sprague-Dawley albino rats of three different age ranges were studied. Studies were completed in 5 young adult rats, aged 4 to 6 months, obtained from Taconic Farms (Germantown NY), 7 middle-aged rats, 14 to 16 months old, and 6 aged rats, 3 at 26 and 3 at 36 months of age, obtained from Charles River Breeding Laboratories (Wilmington MA). The animals were maintained on Purina Laboratory Chow and water *ad libitum* until fourteen hours prior to the study, at which time they were deprived of food.

Determination of Regional Cerebral Glucose Consumption

Rates of local cerebral glucose consumption were determined by means of the autoradiographic [^{14}C]deoxyglucose method. A detailed description of the theory and procedure of this method has been published (Sokoloff *et al.*, 1977). Briefly, the method is based on the use of 2-deoxy-D-[1-^{14}C]glucose as a tracer to measure glucose utilization. This analogue competes with glucose for transport across the blood-brain barrier and for phosphorylation by hexokinase in the brain tissue. Once phosphorylated, however, it remains trapped in the cells for the duration of the procedure. By analysis of the kinetics of the exchange of deoxyglucose and glucose between plasma and brain tissue and their phosphorylation by brain hexokinase, an operational equation has been derived which permits the calculation of local rates of glucose utilization from the time courses of the [^{14}C]deoxyglucose and glucose concentrations in arterial plasma and the local ^{14}C concentrations in the tissues at the time of killing, which are measured by a quantitative autoradiographic technique (Sokoloff *et al.*, 1977).

The animals were prepared for the experiment by the insertion under light halothane anæsthesia of polyethylene catheters into one femoral vein and artery. The rat's hindquarters were then restrained by the application of a loose-fitting plaster cast which was taped to a lead brick. After a period of four to five hours for recovery from the effects of anæsthesia, rates of local cerebral glucose utilization were determined under normal ambient laboratory conditions of sound and light. The procedure was initiated by the administration of an intravenous pulse of 2-deoxy-D-[1-^{14}C]glucose (125 μCi/kg body weight). Timed arterial blood samples were then collected during the following forty-five minutes for the determination of plasma concentrations of glucose and [^{14}C]deoxyglucose. At the end of the forty-five-minute period the rats were killed by an intravenous injection of sodium pentobarbital, and the brains were removed and frozen in isopentane cooled to −40° C with dry ice. The brains were cut into sections, 20 μm in thickness, in a cryostat maintained at −22° C, and the sections were dried and autoradiographed as previously described (Sokoloff *et al.*, 1977). Optical densities of regions of the autoradiographs corresponding to selected cerebral structures were measured with a Photoscan System P-1000 densitometer (Optronics International, Inc., Chelmsford MA). These optical densities were used to determine the local tissue concentrations of ^{14}C by comparison with the optical densities obtained with calibrated ^{14}C-labelled methylmethacrylate standards. From the time courses of the concentrations of [^{14}C]deoxyglucose and glucose in the plasma and the local tissue concentrations of ^{14}C, local rates of glucose consumption were calculated by means of the operational equation of the method (Sokoloff *et al.*, 1977). Calculations were carried out with a PDP 11/34 computer (Digital Equipment Corp., Maynard MA). The autoradiographs were transformed into quantitative colour-coded maps of the distribution of the local rates of glucose utilization by means of a recently developed image-processing system designed for the analysis of autoradiographs and data obtained with the [^{14}C]deoxyglucose method (Goochee, Rasband and Sokoloff, 1980).

Physiological Measurements

The physiological state of the animals at the time of the study was assessed by monitoring a number of variables. Rectal temperature was measured with a YSI Model No. 73 Tele-Thermometer (Yellow Springs Instrument Co., Yellow Springs OH). Mean arterial blood pressure was measured by means of an air-damped mercury manometer attached to the femoral arterial catheter. Hæmatocrit was determined from arterial blood samples collected in capillary tubes and centrifuged in a Beckman Microfuge B (Beckman Instruments, Fullerton CA). Arterial blood pH, pCO_2 and pO_2 were measured in an ILS Model No. 213 Blood Gas Analyzer (Instrumentation Laboratory, Inc., Lexington MA).

Statistical Analyses

Comparisons of data obtained in the three groups were analysed for statistical significance by Bonferroni t tests for multiple comparisons (Miller, 1966).

RESULTS

Survival

The middle-aged and aged groups of rats used in the studies were derived from a population of retired breeders segregated specifically for ageing research at the age of 11 months. At the ages of 15, 26 and 36 months the survival rates of the populations were about 100, 70 and 50 per cent, respectively (Dr Puczak, Corporate Director, Veterinary Services, Charles River Breeding Laboratories, personal communication). Of a total of 17 animals obtained from the Charles River

Laboratories one of the 26-month-old rats died, and one each of the 15-, 26- and 36-month-old animals was excluded from the study because of severe hypotension during the experimental procedure. Thus, the 15-, 26- and 36-month-old rats included in this study represent approximately 88, 42 and 38 per cent, respectively, of the original rat population. Because of the losses of animals and consequent small numbers in the 26- and 36-month-old age groups, these groups were combined into a single 'aged' group to facilitate statistical analyses of the data. There were no significant differences between the local rates of glucose utilization in these two groups, except in the parietal cortex where the values for the 26- and 36-month-old rats were 98±3 and 86±2 (mean ±SEM, $P < 0.05$) μmol glucose/100 g/min, respectively. In the supragranular zone of the dentate gyrus and the caudate-putamen the difference between the mean values of the two aged groups approached statistical significance ($0.1 > P > 0.05$); as in the parietal cortex the mean values in these regions were 12 to 20 per cent lower in the 36-month-old rats than in the 26-month-old rats.

TABLE 1. PHYSIOLOGICAL VARIABLES IN RATS OF DIFFERENT AGES DURING MEASUREMENT OF LOCAL CEREBRAL GLUCOSE UTILIZATION§

Parameter	*Young adult* (*5*)	*Middle-aged* (*7*)	*Aged* (*6*)
Body weight (g)	410±6	605±32**	630±47*
Hæmatocrit (%)	51.4±0.6	51.7±0.8	50.5±1.2
Mean arterial blood pressure (mm Hg)	120±3	118±2	119±4
Arterial blood pH	7.46±0.02	7.40±0.03	7.44±0.02
Arterial blood pO_2 (mm Hg)	85.3±2.4	87.6±1.6	90.0±1.1
Arterial blood pCO_2 (mm Hg)	33.4±0.9	33.4±1.0	36.2±1.5
Arterial plasma glucose (mg %)	160±5	159±10	151±10

§ The values are the means ± standard errors obtained in the number of animals indicated in parentheses. * Significantly different from young adult rats; $P < 0.05$. ** Significantly different from young adult rats; $P < 0.01$.

Physiological Status

There were no apparent significant differences in the physiological status of the three groups of animals (Table 1). Only body weight exhibited an age-related change; body weight was increased in the middle-aged and aged rats in comparison with the young adult group.

Average Rates of Glucose Utilization in Brain as a Whole

The mean rates of glucose utilization for the brain as a whole were calculated from the local values of all the brain structures weighted for their volumes. In comparison with the young adult rats, average brain glucose utilization in both the middle-aged and aged animals was significantly reduced by 21 and 17 per cent, respectively (Table 2).

TABLE 2. AVERAGE CEREBRAL GLUCOSE UTILIZATION IN BRAIN AS A WHOLE§

Age of rats	*Weighted average cerebral glucose utilization (μmol/100 g/min)*
Young adult (4)	77±2
Middle-aged (7)	61±2**
Aged (6)	64±4*

§ The values are the means ± standard errors obtained in the number of animals indicated in parentheses. * Significantly different from young adult rats; $P < 0.05$. ** Significantly different from young adult rats; $P < 0.01$.

Local Rates of Cerebral Glucose Utilization

Local rates of glucose utilization were determined in 47 cerebral structures. For the purpose of presentation these structures have been grouped according to the functional systems with which they are presumed to be associated.

Rates of glucose utilization were determined in two regions of brain that may be involved with associative or integrative functions, for example, the frontal and parietal cortex (Table 3). No statistically significant effects of age were found in the

TABLE 3. CEREBRAL STRUCTURES INVOLVED IN ASSOCIATIVE AND INTEGRATIVE FUNCTIONS

	Local cerebral glucose utilization§ (μmol/100 g/min)		
Structure	*Young adult (5)*	*Middle-aged (7)*	*Aged (6)*
Frontal cortex (cortical area 10)	96±5	85±3	88±4
Frontal cortex, layer IV	111±6	98±4	99±5
Parietal cortex (cortical area 7)	116±11	85±3**	92±3*
Parietal cortex, layer IV	131±9	94±3**	100±4**

§ The values are the means ± the standard errors obtained in the number of animals indicated in parentheses. *Significantly different from young adult rats; $P < 0.05$. **Significantly different from young adult rats; $P < 0.01$.

frontal cortex, but in the parietal cortex the rates of glucose consumption were significantly lower (by about 25 per cent) in both the middle-aged and aged rats in comparison with the young adults. In the limbic system (Table 4) the only significant age-associated reduction was found in the supragranular zone of the dentate gyrus.

TABLE 4. LIMBIC SYSTEM

Structure	Local cerebral glucose utilization§ (μmol/100 g/min) Young adult (5)	Middle-aged (7)	Aged (6)
Hippocampus			
Ammon's horn	73±4	62±3	69±3
Dentate gyrus	69±6	61±2	70±3
Dentate gyrus—supragranular zone	68±3	55±2*	64±3
Stratum lacunosum moleculare	88±4	77±4	83±4
Amygdala	55±3	49±4	48±2
Septal nucleus	53±4	44±4	50±1
Nucleus accumbens	88±9	66±3	73±2
Hypothalamus	53±7	49±3	51±1
Mamillary body	113±7	107±3	112±8

§ The values are the means ± standard errors obtained in the number of animals indicated in parentheses. * Significantly different from young adult rats; $P < 0.05$.

In nearly all the structures of the visual (Table 5) and auditory systems (Table 6) the values in both the middle-aged and aged rats were 15 to 30 per cent lower than those in the young adult animals. In the olfactory (Table 6) and somatosensory systems (Table 7) age-related differences were not so widespread, and fewer structures exhibited statistically significant changes. There were also significant age-related decreases in glucose metabolism in most of the myelinated fibre tracts that were examined (Table 8).

Some of the results presented in Tables 3–8 are best illustrated in quantitative colour-coded transformations of the autoradiographs. Fig. 1 contains such transformed autoradiographs of sections of brain at four different levels obtained from rats representative of each age group. The colour bar on the right provides the calibration scale for the values of glucose utilization in μmol/100 g brain/min represented by each colour. Identification of some of the structures visualized in the autoradiographs is facilitated by the diagrammatic representations of the autoradiographs obtained in young adult rats (fig. 2). These colour-coded maps provide a detailed view of the localized effects of ageing beyond those practically described in tabular form. For example, at all four levels illustrated, and especially at the level of

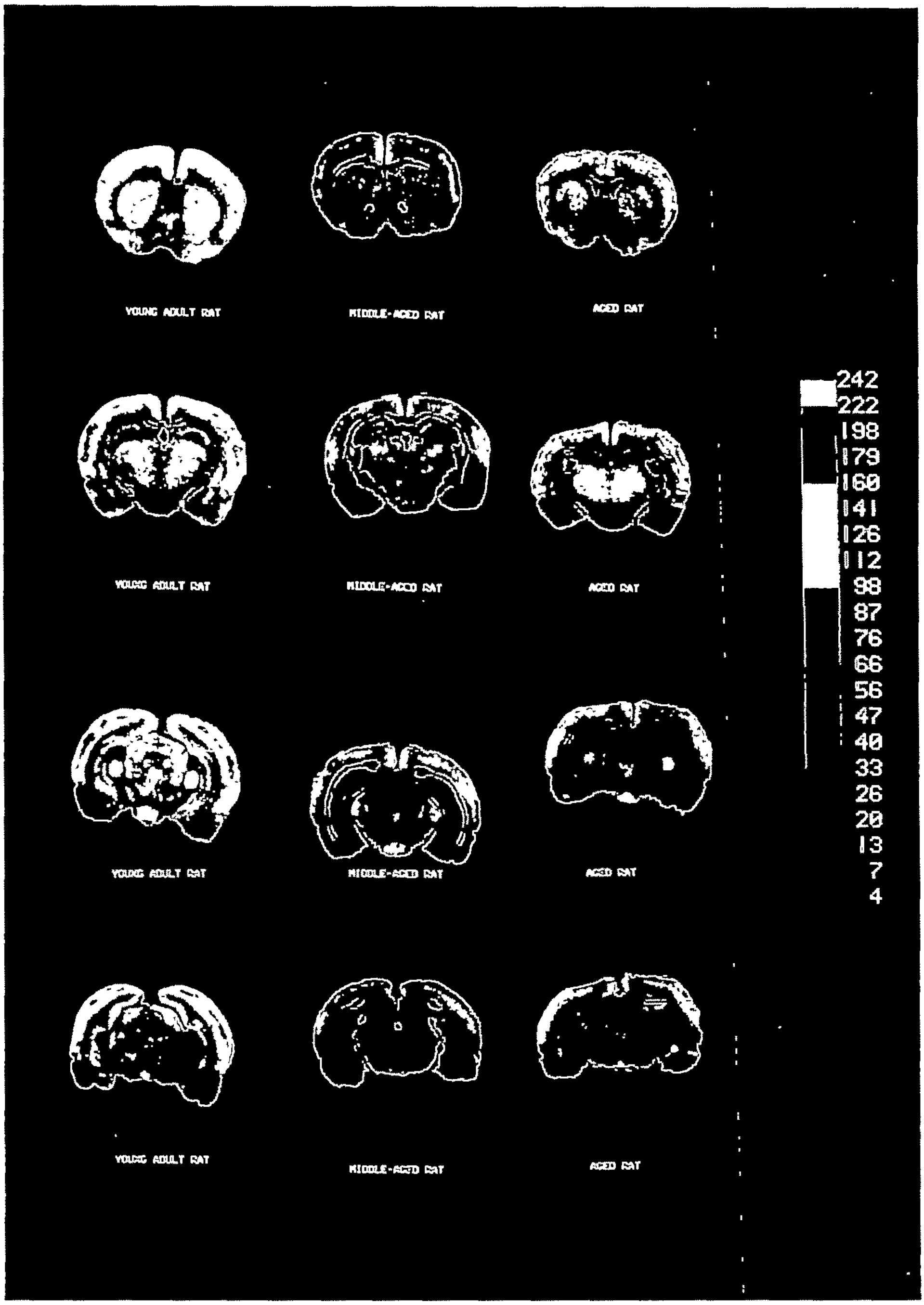

FIG. 1. Colour-coded quantitative transformations of autoradiographs from rats representative of three age groups at four different levels in the brain. The age groups represented are from left to right: young adult (4 to 6 months), middle-aged (14 to 16 months) and aged (26 to 36 months). The sections from top to bottom were taken at the level of the head of the caudate-putamen, the thalamus, the medial geniculate body and the superior colliculus. Specific structures are identified in the diagrammatic representations shown in fig 2. The colour bar on the right provides the calibration scale for the range of values of glucose utilization in μmol/100 g/min for each colour.

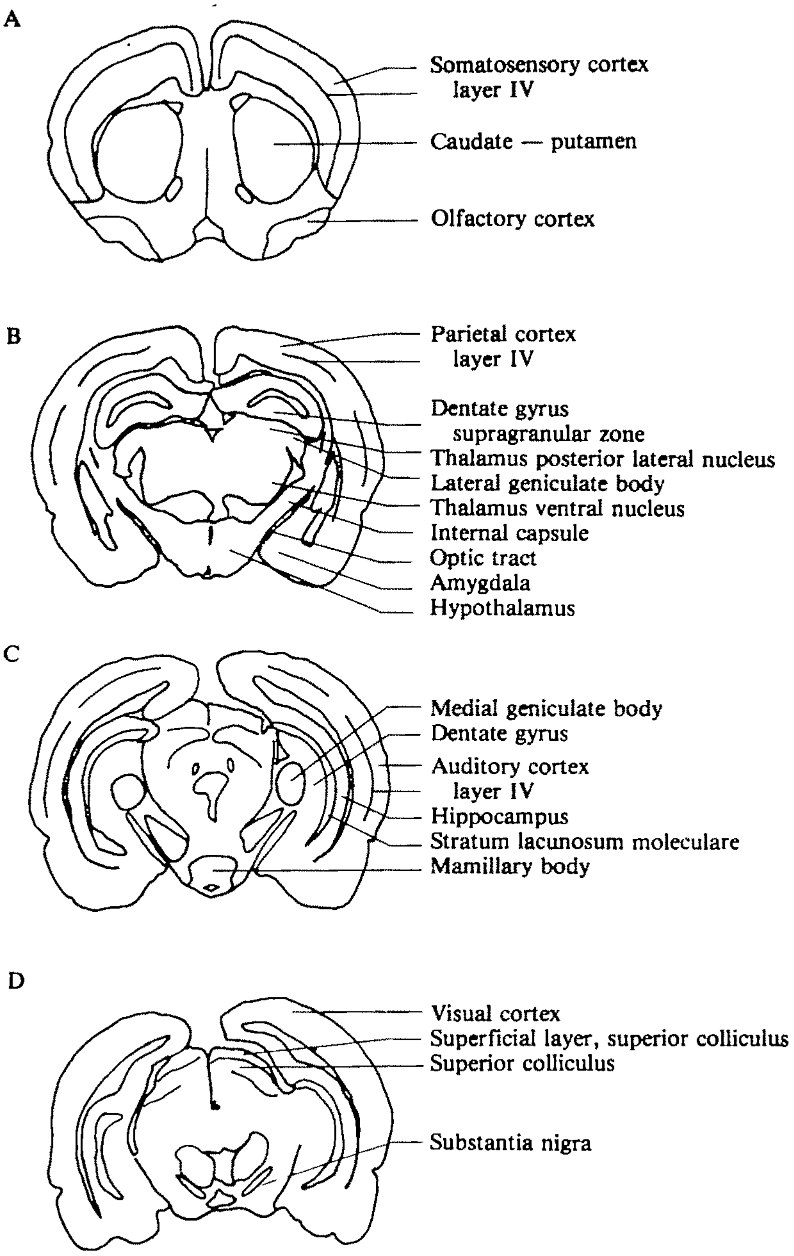

FIG. 2. Diagrammatic representations of the autoradiographs shown in fig. 1. A, diagrammatic representation at the level of the head of the caudate-putamen. B, diagrammatic representation at the level of the thalamus. C, diagrammatic representation at the level of the medial geniculate body. D, diagrammatic representation at the level of the superior colliculus.

TABLE 5. VISUAL SYSTEM

Structure	Local cerebral glucose utilization§ (*μmol/100 g/min*) *Young adult* (*5*)	 *Middle-aged* (*7*)	 *Aged* (*6*)
Visual cortex (cortical area 17)	117±7	86±3**	90±4**
Visual cortex, layer IV	128±8	91±4**	96±4**
Lateral geniculate body	96±7	74±3*	84±5
Superior colliculus	92±2	75±2**	74±3**
Thalamus: posterior lateral nucleus	107±5	84±4**	101±5

§ The values are the means ± standard errors obtained in the number of animals indicated in parentheses. * Significantly different from young adult rats; $P < 0.05$. ** Significantly different from young adult rats; $P < 0.01$.

TABLE 6. AUDITORY SYSTEM

Structure	Local cerebral glucose utilization§ (*μmol/100 g/min*) *Young adult* (*5*)	 *Middle-aged* (*7*)	 *Aged* (*6*)
Auditory cortex (cortical area 41)	139±9	120±6	121±4
Auditory cortex, layer IV	169±8	138±7*	138±4
Medical geniculate body	125±3	105±4	108±5
Inferior colliculus	184±8	149±4**	148±8
Lateral lemniscus	112±4	100±3	86±5
Superior olivary nucleus	133±7	115±3	106±3
Cochlear nucleus	130±17	119±1	107±6

OLFACTORY SYSTEM

Structure	Local cerebral glucose utilization§ (*μmol/100 g/min*) *Young adult* (*5*)	 *Middle-aged* (*7*)	 *Aged* (*6*)
Olfactory cortex (cortical area 51)	122±5	103±7	106±6

§ The values are the means ± the standard error obtained in the number of animals indicated in parentheses. * Significantly different from young adult rats; $P < 0.05$. ** Significantly different from young adult rats; $P < 0.01$.

the parietal cortex, it can be seen that cortical layer IV is strikingly reduced with respect to both extent and rate of glucose consumption in the two older groups of rats. Furthermore, the entire cortex appears to be somewhat thinner in the aged animals than in the young adult and middle-aged rats. At the level of the medial geniculate body the superficial layer of the superior colliculus is clearly evident in the section from the young adult rat, whereas in the sections from the older animals it is not discernible.

TABLE 7. SENSORIMOTOR SYSTEMS

	Local cerebral glucose utilization§ (μmol/100 g/min)		
Structure	*Young adult* (5)	*Middle-aged* (7)	*Aged* (6)
Somatosensory cortex (cortical area 2)	111±4	95±3	97±6
Somatosensory cortex, layer IV	134±4	113±4*	116±7
Inferior olivary nucleus	92±9	67±2**	68±4**
Gracile and cuneate nuclei	74±4	60±4*	62±3
Cerebellar cortex	53±3	50±1	53±2
Cerebellar nuclei	98±8	88±2	94±5
Spinal grey matter	52±2	47±2	55±4
Pontine grey matter	59±4	51±1	52±2
Thalamus: ventral nucleus	98±6	78±2	92±6
Vestibular nucleus	114±8	104±3	100±4
Extrapyramidal system			
Caudate-putamen	103±4	86±3**	88±3*
Globus pallidus	57±4	46±2*	56±2†
Substantia nigra	62±4	55±2	58±3

§ The values are the means ± standard errors obtained in the number of animals indicated in parentheses. * Significantly different from young adult rats; $P < 0.05$. ** Significantly different from young adult rats; $P < 0.01$. † Significantly different from middle-aged rats; $P < 0.05$.

DISCUSSION

The results of these studies demonstrate that in the resting conscious rat ageing *per se* is associated with decreases in glucose utilization in specific regions of the brain. The changes are clearly selective and have a predilection for certain neural systems. The local rates of cerebral glucose utilization do not appear to change progressively with age. In general, the decreases were already observed in the rats 14 to 16 months of age with no further change in those 26 to 36 months of age. It is likely that this apparent lack of progression is a reflection of the influence of a survival effect (Schaie, 1977), a common sampling artefact in cross-sectional studies of ageing. The 26- to 36-month-old rats included in this study represent a population of only 40 per cent that survived from the original rat population; they may have, therefore, represented a selected sample of survivors that aged at a slower rate.

TABLE 8. MYELINATED FIBRE TRACTS

Structure	*Local cerebral glucose utilization§ (μmol/100 g/min)* *Young adult* (5)	 *Middle-aged* (7)	 *Aged* (6)
Corpus callosum	39±3	27±1**	30±2*
Genu of corpus callosum	24±2	22±2	26±1
Anterior commissure	40±2	32±2*	39±1
Optic chiasma	28±6	16±2*	22±1
Optic tract	31±5	24±5	23±4
Hippocampal fimbria	29±3	20±2*	25±1
Spinal white matter	—	17±2	18±1
Cerebellar white matter	41±1	28±1**	32±2**†

§ The values are the means ± standard errors obtained in the number of animals indicated in parentheses. * Significantly different from young adult rats; $P < 0.05$. ** Significantly different from young adult rats; $P < 0.01$. † Significantly different from middle-aged rats; $P < 0.05$.

In this study in which the rats were maintained under ambient laboratory conditions of light and sound the brain structures that are selectively affected with ageing include those associated with vision and audition. The entire visual system (Table 5) is particularly severely affected. These changes may reflect an age-related primary retinal degeneration which has been demonstrated in both Fisher 344 (Lai, Jacoby and Jones, 1978) and Sprague-Dawley rats (Schardein, Lucas and Fitzgerald, 1975). It has been shown that in the albino rat, in which the visual system is 80 to 85 per cent crossed at the optic chiasma, unilateral enucleation results in marked reductions in glucose consumption in all the components of the visual system on the contralateral side (Kennedy, Des Rosiers, Jehle, Reivich, Sharpe and Sokoloff, 1975). The auditory system is also affected in the aged animals (Table 6) although the changes are not so pronounced as those in the visual system. Auditory deprivation in the Sprague-Dawley rat due to either occlusion of the external auditory canals with wax or otitis media has been shown to result in marked (35 to 60 per cent) reductions in glucose consumption in the brain structures associated with audition (Sokoloff, 1977). Although no data are available concerning degenerative changes in the cochlea of aged rats, such changes occur in man with senescence in association with a loss of hearing (Corso, 1977). Losses of pyramidal cell dendritic spines, which have been demonstrated in both the visual (Feldman, 1976) and auditory (Vaughan, 1977) cortices as a function of age, may also result from a partial functional deafferentation.

In the sensorimotor systems (Table 7) the most noteworthy changes occur in the extrapyramidal system, inferior olivary nucleus, and in the gracile and cuneate nuclei. The cuneate and gracile nuclei were examined for changes in glucose utilization because it has been reported that axonal dystrophy is prevalent in these nuclei (Fujisawa and Shiraki, 1978), which are two of the major sensory relay nuclei and contain the nerve-endings from some of the longest axons in the central nervous system. In the gracile nucleus of the rat, axonal dystrophy begins by 7 months of age and reaches a plateau at 10 months (Fujisawa and Shiraki, 1978). Our findings of a 20 per cent reduction in glucose consumption in these nuclei are consistent with these neuropathological changes. The extrapyramidal motor system is also a prominent site of change with senescence. Signs of parkinsonism are common in normal aged human subjects (Beasley and Ford, 1976), and movement disorders which can be reversed by dopamine agonists have been observed in aged rats (Marshall and Berrios, 1979). Changes with age in dopamine turnover (Finch, 1973), the number of dopamine receptors (Makman, Ann, Thal, Sharpless, Dvorkin, Horowitz and Rosenfeld, 1979), and the dopamine sensitivity of adenylate cyclase (Govoni, Loddo, Spano and Trabuchi, 1977; Puri and Volicer, 1977) in the striatum of mice, rabbits and rats, respectively, are well documented. The decreased rate of glucose consumption in the inferior olivary nucleus found in the older groups of animals may also be related to dopaminergic innervation of this nucleus. The effects of apomorphine, a dopamine agonist, on glucose utilization are presently being examined, in order to ascertain whether structures with dopaminergic innervation, such as the caudate-putamen and the inferior olivary nuclei, can be metabolically activated by dopamine agonists in aged animals. The preliminary results suggest that there is indeed a reduced sensitivity to apomorphine in some selected structures with ageing.

The limbic system, particularly the hippocampus, was examined in detail because it has been implicated in learning and memory in human subjects (Milner, 1959) and, perhaps, also in rodents (Weizkrantz and Warrington, 1975). In the human brain the hippocampus is the site of many age-related histopathological changes, such as senile plaques, neurofibrillary tangles, and granulovacuolar degeneration (Corsellis, 1962; Tomlinson, Blessed and Roth, 1968), and the extent of these changes in demented old people can be correlated with the extent of the memory deficit in the subject (Blessed, Tomlinson and Roth, 1968). Although these particular neuropathological changes do not occur in the rat (Dayan, 1971), decreases in the number of synapses have been found in aged rats (Geinisman, Bondareff and Dodge, 1977; 1978). In the present study the rate of glucose utilization throughout the limbic system appeared to remain quite normal with age. The only significant decrease was found in the supragranular zone of the dentate gyrus of the middle-aged group; it is in this specific area that Geinisman *et al.* (1977; 1978) found losses of synaptic terminals and dendrites in rats.

The finding of a significant decrease in glucose utilization in the parietal cortex (Table 3) of the aged animals may be one of the most interesting results of this study. In the rat this cortical region (area 7) is one of the few known associative areas in the cortex (Krieg, 1946). The decreased glucose utilization in this area may reflect decreased sensory input.

The local rates of glucose utilization in the brain have been shown to be closely correlated with local functional activity (Sokoloff, 1977). Decreased glucose utilization may reflect decreased functional activity as well as degenerative or pathological changes in the region affected. Some of the changes in glucose utilization observed in the older rats may have been due to either reduced functional activity, pathological damage, or both. When the decreases in glucose utilization are observed in nearly all the structures of a pathway, as, for example, in the auditory and visual systems, then it is likely that there is decreased functional activity in the system, perhaps due to reduced input into the pathway. Decreases in glucose utilization in single structures of a pathway may be indicative of pathological changes within the structures themselves.

SUMMARY

The effects of ageing on local rates of glucose utilization in 47 brain structures in resting conscious rats have been examined. Three age groups have been studied: young adult (4 to 6 months), middle-aged (14 to 16 months), and aged (26 to 36 months). The results show that ageing *per se* is associated with decreases in rates of glucose utilization in specific brain regions. The decreases were not progressive with age, probably because of the influence of a survival effect. Age-related pathological changes are known to occur in some of the brain structures in which decreases in rates of glucose utilization were found. Selective decreases were also found in the caudate-putamen, the parietal cortex and in structures associated with vision and audition. In these latter structures the changes may reflect reductions in local functional activity, perhaps due to decreased sensory input from the primary sensory organs.

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MUSIC AND LANGUAGE

MUSICAL ALEXIA AND AGRAPHIA

by JOHN C. M. BRUST

(From the Department of Neurology, Harlem Hospital Center and Columbia University College of Physicians and Surgeons)

INTRODUCTION

MUSIC, 'the art or science of arranging sounds in notes and rhythms to give a desired pattern or effect' (Jacobs, 1967), joins language differently in song, recitative, chant, sprechstimme, poetry, the inflection of everyday speech, and, of course, musical notation (Critchley, 1972; Henson, 1977*a*, *b*). Amusia and aphasia occur alone or together, and prosody, which includes the musical elements of pitch, rhythm and stress, and which gives both propositional and emotional meaning to speech, may be altered in aphasics who retain ability to sing and to appreciate music (Monrad-Krohn, 1947). There appears to be left hemispheric dominance for identifying words whose meaning depends upon pitch (Van Laucker and Fromkin, 1973), whereas identification of the emotional context of speech seems to require the right hemisphere (Tucker, Watson and Heilman, 1977). Musical stimuli have precipitated seizures in patients with either right or left hemispheric lesions (Scott, 1977), and seizures generated from either hemisphere may include musical hallucinations (Mulder and Daly, 1952). In epileptics (Penfield and Perot, 1963), hallucinated music or spoken voices followed stimulation of either temporal lobe, and there was no topographical difference between areas associated with voices and those associated with music.

Music is usually non-propositional, yet appreciation of music may be more intellectual than emotional. Although most people enjoy music, some lack the fundamental skill of either recognizing or reproducing simple melodies or even single intervals. A majority are musically illiterate, although they may be musically talented. Few have absolute pitch in the accepted sense of the term. The elements of music—pitch, timbre, duration, loudness and rhythm—are separable, and recognition of sounds in a chord is horizontally non-linear, in contrast to recognizing melody. Musical notation includes both verbal and non-verbal elements and indicates both simultaneous and serial events.

It is not surprising, therefore, that studies of music and language, and attempts to localize and to classify amusia, have been conflicting. Henschen (1920, 1925, 1926) considered amusia, like aphasia, to be either motor (vocal and instrumental amusia and musical agraphia) or sensory ('music deafness', 'amnestic amusia' and musical alexia). On the basis of autopsy studies he believed centres for particular musical functions existed in the language-dominant hemisphere, for example a 'singing centre' in the pars triangularis of the third frontal convolution, a receptive music centre at the temporal pole, a note-reading centre near the angular gyrus and an instrumental centre at the foot of the second frontal convolution (although there appeared to be a special centre for violinists). Despite this rigidly anatomical approach, Henschen (1926) observed 'Musical faculty is phylogenetically as well as ontogenetically older than speech, and its representation is more uniformly distributed over both hemispheres'. Preserved musical function in the presence of aphasia he attributed to right hemispheric takeover.

Kleist (1928) divided motor and sensory amusias into those affecting either tone or melody, and placed the responsible lesions in the left hemisphere. 'Tone muteness', for example, he attributed to destruction of the lower third of the left anterior central convolution, between centres for singing and for whistling. On the basis of a single autopsy case of normal musical function and destroyed temporal tips, Kleist discounted their importance in musical reception. Feuchtwanger (1930), more interested in the neuropsychology of music and speech than in anatomical localization, observed that language and music each had symbolic and non-symbolic aspects and predicted that bilateral cortical activity was involved in the production and understanding of each. Although aphasia was present in each of his 34 amusic patients, he acknowledged that phonemic and melodic perception could be lost independently. Ustvedt (1937), noting the heterogeneity of amusic patients and the frequent failure of investigators to determine premorbid musical capacity or to use standardized tests, stressed '... how slight the possibility of localization is in the majority of cases and how unjustifiable it is to draw conclusions regarding the normal localization of a given function from the localization of a lesion associated with a particular defect'. He also criticized the neuropsychological views of Feuchtwanger as 'theoretical and artificial'.

Hécaen (1962) believed right hemispheric lesions caused difficulty with sound recognition, whereas left-sided lesions resulted in 'a disorganization of musical understanding'. Wertheim (1969, 1977) believed receptive amusia was most often due to lesions of the language-dominant hemisphere, whereas expressive amusia followed non-dominant hemispheric damage, the second frontal convolution in the case of instrumental amusia and the pars triangularis with vocal amusia. Damasio and Damasio (1977) accepted right hemispheric dominance for 'musical execution' but believed musical perception shifted from the right to the left hemisphere as a person became increasingly sophisticated musically. Benton (1977) noted that expressive amusia was associated with anterior lesions and receptive amusia ('defects in the perception and recognition of tones and melodies ... with or without concomitant expressive impairment') was caused by temporal lobe disease, but that either kind of amusia could follow damage to either hemisphere.

The two present cases demonstrate the prematurity of broad generalizations regarding either music and language or hemispheric specialization for musical function. Each was a professional musician, able to read and write music, in whom aphasia was accompanied by disturbed musical function, but of very different kind and degree, including musical alexia and agraphia.

PATIENTS AND METHODS

To minimize fatigue both patients were examined in short sessions seldom exceeding an hour. For language testing the manual of Goodglass and Kaplan (1972) was used. For musical testing Wertheim's (1969) procedure was used, and additional tests of musical alexia and agraphia were added. These included playing written single notes; playing or singing written intervals; matching written intervals with what was heard; observing whether a written interval was upward or downward; tapping out written rhythms; drawing specific notes, clefs and rests; indicating pitch on a score; and writing heard intervals.

Case 1

In February 1976 a 22-year-old music student was admitted to hospital for partial complex, right focal motor, and generalized seizures. Neurological examination was normal, but carotid angiography revealed a lemon-sized meningioma beneath the left temporal lobe. During attempted total removal, unexplained massive left temporal swelling developed; emergency right craniotomy and dural incision failed to reveal hæmatoma or swelling on that side. To allow skin closure, left hemicraniectomy and anterior temporal lobectomy were performed. She left the operating room breathing spontaneously but with both pupils dilated and unreactive to light.

Within several hours pupillary reactivity returned, and a few days later she was awake, with right hemiplegia and sensory loss, right homonymous hemianopia and global aphasia. At re-operation the left cerebral convexity was still swollen and discoloured. No significant hæmatoma was apparent, and the dura was closed with a fascia lata graft. Over the next few weeks her strength improved, and speech gradually became fluent, consisting largely of paraphasic jargon; there was little evidence of language comprehension. Deterioration attributed to hydrocephalus led to placement of a right ventriculo-atrial shunt through the right frontal lobe, following which improvement resumed.

In November 1976 computerized tomography revealed a large low density area in the posterior temporo-parietal area, consistent with infarction, plus an inferior contrast-enhanced lesion which was believed to represent residual neoplasm (fig. 1). Following uncomplicated total removal of the meningioma she had several major motor, partial complex, and right sensory seizures, controlled with phenytoin and carbamazepine. During the next eighteen months, the aphasia gradually improved, and strength became normal. Alexia and agraphia remained severe, and her visual field defect and sensory loss persisted. Resuming her studies, she received a degree of Bachelor of Music in May 1978.

Always right-handed, she had learned how to read music with the guitar in early adolescence and had begun singing lessons at the age of 14 years and piano lessons at the age of 15 years. When she was first admitted, during her fourth year of professional study, she could sightread madrigals by voice and Chopin waltzes on the piano and often wrote out musical parts. She did not have absolute pitch.

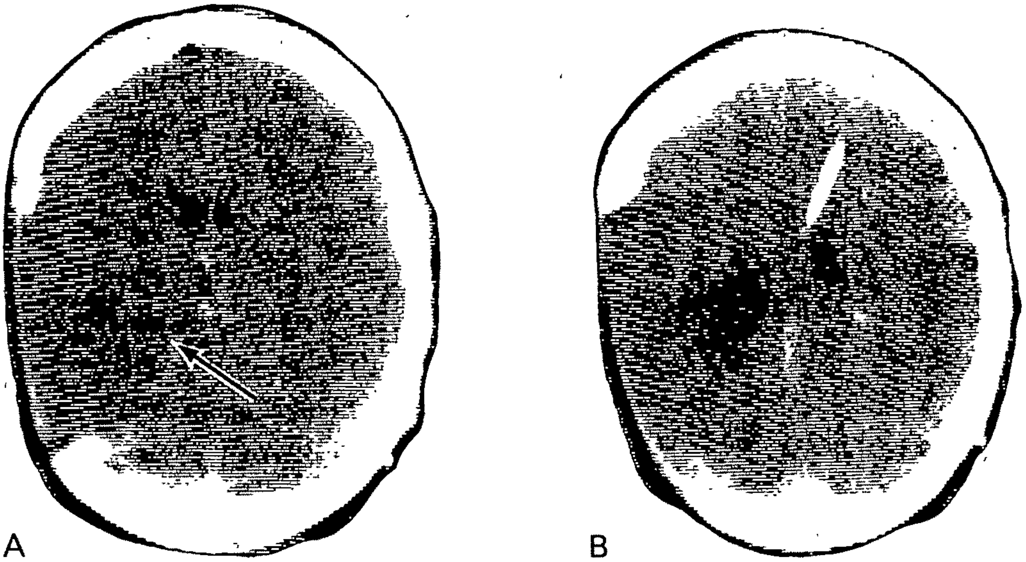

FIG. 1. *Case 1.* CT scan. A, left inferior temporal lobe lucency, consistent with infarction, plus contrast-enhancing residual meningioma (arrow). B, temporo-parietal lucency. Amputated left anterior temporal lobe is not demonstrated.

Even while severely aphasic she enjoyed listening to music and later said that in contrast to her language difficulties, musical understanding never seemed impaired. Similarly, although she had often been aware of paraphasic errors when she spoke, she believed she had, from her first attempts at singing, sung the notes properly and with fewer paraphasic errors. Unable to read or write either words or music, she memorized new songs by listening to recordings. Right hand clumsiness prevented piano playing, and so she returned to the guitar, using her left hand for finely coordinated chord placement and her right hand for coarse but properly rhythmical strumming; individual string plucking was too difficult for her.

Language and music testing (*July 1977*). Despite paraphasic errors, her spontaneous speech was intelligible. Prosody was normal. Auditory comprehension was especially impaired for body parts, prepositions, passive subject-object discrimination, possessive relationships, and complex ideational material. Naming produced verbal paraphasic errors, and she named only six animals in one minute. Word and phrase repetition led to only occasional literal paraphasias, usually self-corrected, and she was able to repeat syntactically complex phrases (for example, 'no ifs, ands, or buts'). Reciting the days of the week and the months, she omitted Saturday and December. Literal and verbal paraphasias contaminated recitation of nursery rhymes and the words of familiar songs.

Reading single words and sentences aloud produced many literal and verbal paraphasias, for example, 'sammock' for 'hammock', and 'atomic' for 'explode'. Written language comprehension was more severely impaired than reading aloud. She mis-identified most written words after hearing them spoken and mis-named most words spelled orally. Selecting written words to complete written sentences or to answer questions about written paragraphs revealed severe disability. Word-picture matching, on the other hand, was normal; she pointed to the correct pictured object, geometrical shape, number, colour, or action for the written word shown, including those she had read paraphasically or said she could neither read aloud nor understand.

She wrote her name correctly but not her address; 'Fair Hill Road' became 'Fa Ro'. Transcribing printed sentences into script was done clumsily but correctly. Writing the alphabet and numbers up to 21, she did the first few correctly and then made paragraphic errors, omissions and repetitions. She correctly wrote most dictated letters and numbers, but could write no more than the first letter of any dictated word or the name of something seen. Attempting to describe the cookie theft picture, she wrote, 'she m . . . .', and then could write no more.

There was neither left-right confusion nor finger agnosia. Simple calculation, spoken and written, was poor, even when she understood the number involved. There was no apraxia. Copies of simple diagrams, including a Necker cube, and spontaneous drawings of a clock and a flower were normal, and there was no hemi-inattention.

Summary. She had moderately severe transcortical sensory aphasia. Repetition, though not normal, was much less impaired than auditory comprehension. Alexia and agraphia were marked, yet semantic understanding of written words appeared intact as far as matching them to pictures was concerned.

Non-lexic receptive musical appreciation was normal for tone, melody, and harmony. She correctly identified the higher or lower of two pitches, including half-tones. Single tones played on a piano were correctly sung. She identified a variety of well-known melodies either sung or played to her, and was aware of intentional errors. She correctly identified by naming or by imitation musical instruments from recordings. Identification of serially and simultaneously played intervals was correct within the limits of anomia. Major and minor chords, the number of notes in a chord (up to four), and intervals in chords (if arpeggio) were identified. She recognized 3/4 and 4/4 metre and correctly reproduced rhythms tapped, played on a single piano note, or bound to a melody. Fast *vs* slow, accelerando *vs* ritardando, and crescendo *vs* diminuendo were also identified.

Non-graphic musical expression was also intact. She correctly sang well-known melodies, accompanied and unaccompanied, and with upward and downward key transposition. She could learn new melodies. Ascending and descending scales, legato and staccato, were correctly imitated, and she could sing crescendo, decrescendo, accelerando, and ritardando. With her left hand she could play simple melodies on the piano and make proper chords on the guitar, and she correctly played named piano notes, guitar chords, and intervals. She believed her left-handed instrumental ability was as good as it was before her illness and, singing several current popular songs, correctly accompanied herself on the guitar. When she added words, there were paraphasic errors to the same degree as when she recited rhymes or lyrics, but the melody and rhythm remained correct.

She identified by naming or selection from a list all the notes on a piano keyboard. Naming written single notes was often incorrect, however, and playing written notes on the piano, especially in the bass clef, led to frequent errors. Written intervals and chords were played and sung badly, whether or not she played the first or lowest note correctly, and she could not match written intervals with what she heard. She always recognized, however, whether an interval was upward or downward. Unsuccessfully attempting to sightread simple melodies, she usually heard her errors and attempted self-correction. She recognized whole, half, quarter and eighth notes, time signatures, accidentals and dynamic symbols, including letter abbreviations (*f*, *pp*, etc.). Rhythm was read better than pitch, with only occasional errors tapping simple written patterns, including sixteenth notes, dotted quarters and eighths, and easy syncopation. She figured out guitar chord fingering with her left hand from standard tabulature.

Several lines of a four-part score were correctly copied, including clefs, metre indication, key, measures, rests and notes, and she drew on command whole, half, quarter and sixteenth notes, a treble and a bass clef, and whole, half and quarter rests. She could not, however, indicate pitch on a score. Attempting to write intervals (sung or played), she made frequent errors, but always wrote upward or downward correctly. Writing well-known melodies (named or played) was done laboriously and with errors of note placement and rhythm (fig. 2), especially in the bass clef, and with no improvement when she wrote either element alone.

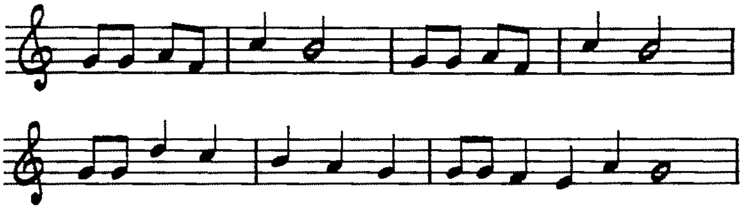

FIG. 2. *Case 1.* Attempt to write 'Happy Birthday', demonstrating errors of note placement and rhythm. (This and subsequent musical illustrations have been transcribed by an artist for clarity.)

In April 1978 she gave a singing recital, which included works in five languages ('Ah, Spietato', by Handel; 'Zwei Lieder', Op. 91, by Brahms; 'Le Bestaire', by Poulenc; 'Cancion De Duna Para Dormir A Un Negrito', by Montsalvatge; and 'Four Songs', based on the poetry of Thomas Campion, by Virgil Thomson). Several of these pieces she had learned since her illness. There were no apparent errors of either music and words, although she believed that there had been occasional paraphasias in the foreign languages, especially German.

Several weeks later aphasia was barely apparent on casual conversation. There were still, however, disturbances in auditory comprehension and naming; repetition was normal. Reading and writing were only mildly improved. She still made frequent verbal paralexias, had considerable difficulty naming words spelled aloud, and missed most of the tests of reading comprehension. Written words were again correctly matched with pictures even when she could neither read them aloud nor give other evidence of comprehending them. She wrote her address better than before ('Fail Hill Rd' for 'Fair Hill Rd'), as well as dictated words and names of objects; but spontaneous written description of the cookie theft picture was limited to 'The gil+the bog'.

Except for reading and writing, musical abilities continued to be normal. She still made errors reading notes, especially in the bass clef, whether using her right or left hand. Written intervals were often incorrectly played or sung, and she tended to ignore sharps and flats, but as before, was correct on upward or downward movement. Although sightreading notes, intervals, and simple melodies was still very difficult, rhythm was now nearly normal. Single notes written to dictation were frequently wrong, especially in the bass clef, and dictated or played intervals or well-known melodies were written nearly as badly as before. Rhythmical elements, however, were much improved (fig. 3), and when she wrote a tune with all notes of the same pitch, rhythm was done correctly.

About this time she embarked on a career singing popular songs (in English) in New York nightclubs. Attending a performance, the author was unable to detect errors of either words or music.

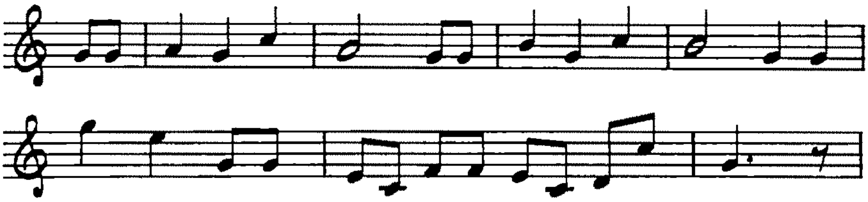

FIG. 3. *Case 1.* Later attempt to write 'Happy Birthday'. There has been greater improvement with rhythm than with note placement; in fact, when she wrote the same tune with all notes of the same pitch, rhythm was correct.

Case 2

A 42-year-old hypertensive man was admitted October 3, 1978, following a major motor seizure. He was initially mute and did not appear to comprehend any speech. There was left gaze preference and right homonymous hemianopia, facial weakness and sensory loss, but he moved his limbs symmetrically, and reflexes were normal. Cerebrospinal fluid (CSF) was grossly bloody, with 52,000 red blood cells per high power field, xanthochromic supernatant, protein 320 mg/dl, and normal glucose content. At left carotid angiography there was an avascular mass in the posterior temporal lobe, plus an aneurysm at an early bifurcation of the middle cerebral artery. Computerized tomography, three weeks after admission, revealed lucency suggestive of infarction in the left posterior temporal and inferior parietal lobes (fig. 4). Recurrent seizures during the first week were effectively treated with phenytoin and phenobarbital, which he took for the remainder of his stay. Improving steadily, he refused operation or further studies and on November 8 signed out against medical advice.

A professional jazz double-bassist, he could read and write music, more easily in the bass than the treble clef. He had been able to sing, but had never done so professionally and did not have absolute pitch. Though not a pianist, he had known where individual notes were on the keyboard.

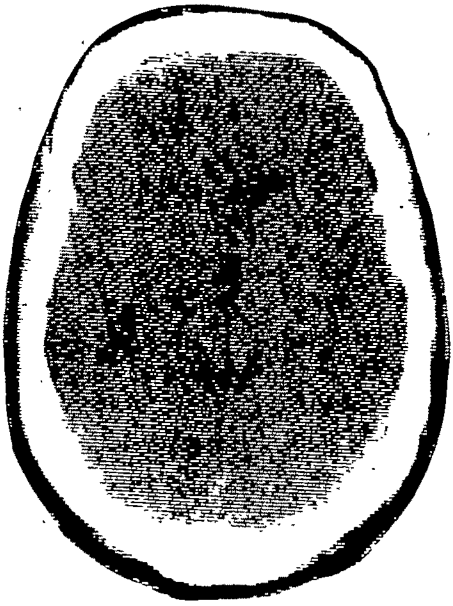

FIG. 4. *Case 2.* CT scan. Left parieto-temporal lucency consistent with infarction.

Language and music testing (*October 16 and 17, 1978*). He was alert, attentive, and co-operative, and had no neurological abnormalities other than aphasia, apraxia and amusia. Spontaneous speech was fluent with normal prosody and infrequent verbal paraphasias, but lacking in substantive content. Describing the cookie theft picture, he said, 'What I see . . . I see the woman . . . beginning to fall . . . I see the person . . . pressure . . . putting places all over the place . . . I see the mess all right.' He comprehended most spoken single words but had difficulty with more complex spoken material. He recited the days of the week and the months, but could count no higher than 12, and, reciting the alphabet, skipped several letters. He could neither recite nursery rhymes and well-known songs nor properly repeat phrases or more than one-syllable words. Grammatical phrases were no worse than non-grammatical. For example, he repeated 'The spy fled to Greece' as 'The spy fights flights', and 'One would have been enough' as 'One were as one'. Naming led to frequent verbal paraphasias.

Reading aloud produced literal and verbal paraphasias, for example, 'tinakel' for 'triangle' and 'How lo go home from worse' for 'I got home from work'. He correctly matched printed and script writing, but had great difficulty matching written and spoken words; there was neither semantic nor phonetic preference in his choices. He failed to identify orally most spelled words. Although there were frequent errors, he selected the correct written word for a picture more often than for a spoken word.

He wrote his name correctly but could write no more than the numerals of his address. He correctly wrote dictated letters and numbers. Transcribing a printed sentence into longhand led to several literal paragraphias, for example, 'bumps' for 'jumps', as did writing words of pictured items, for example, 'squain' for 'square'. He could write no dictated words, saying, 'I forgot my memory'. Shown the cookie theft picture, he wrote only 'fallin'.

Calculation, with the question spoken by the examiner and the answer spoken by the patient, was done poorly, but simple written calculation (addition of three numbers, subtraction, and multiplication) was nearly normal. There was neither left-right confusion nor finger agnosia. Despite his impaired comprehension, it was apparent that he had ideomotor apraxia for many transitive actions: he was unable to imitate use of an object, but performed normally when given it. He was not apractic, however, in showing how to play his double-bass. He copied simple diagrams and put numbers correctly in a clock face, but he could not properly copy a Necker cube.

Summary. He had moderately severe conduction aphasia; repetition was significantly more impaired than auditory comprehension. Alexia and agraphia were marked. Although matching written words with pictures was superior to other reading tasks, he did make errors.

Music did not sound 'right' to him, but he could not elaborate. He was able to tell which of two tones was of higher pitch and to recognize well-known melodies. He identified intentional errors in these tunes and recognized instruments by timbre. He mis-identified most heard intervals, whether trying to name them or to select their names from a list. Similar difficulty occurred recognizing major and minor chords and the number of notes or the intervals in a chord. Attempts to imitate, by singing or whistling, single tones, intervals, or familiar melodies failed, with or without words and whether or not the examiner sang or played along. He would sometimes hit a note correctly but then fall off it; asked if he recognized what he was doing, he replied, 'I can't even hear my voice.' It was thus uncertain to what degree this difficulty was receptive as well as expressive. He appeared unable to recognize metre (e.g. 3/4 *vs* 4/4), and was unable to imitate either dynamic changes or rhythms tapped, played on a single piano note, or bound to a melody.

With written music he correctly named (or selected the name from a list) clefs, quarter, half, and whole notes, accidentals, rests, and time signatures, but not eighth or sixteenth notes or dynamic symbols (including *pp*, *ff*, and non-letter symbols for crescendo and decrescendo). He could neither name, identify, nor play on a piano keyboard written notes in bass or treble clef. He also had great difficulty, however, naming the notes of the piano keyboard, at a time when he had only mild difficulty naming objects, body parts, and colours. He was unable to sing or play simple written intervals, to match heard intervals with what was written, or to imitate written rhythm.

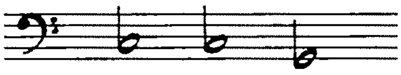

FIG. 5. *Case 2.* Attempt to write 'Happy Birthday' (which he recognized as it was played).

He correctly drew a treble and bass clef and quarter, half and eighth notes. On both treble and bass clef he wrote a C correctly when the name was dictated to him, but misplaced most other notes. He would occasionally write bass clef notes as if they were treble. Starting with C in bass or treble clef, he could not correctly write any intervals heard on the piano. Told to write 'Happy Birthday' (and recognizing it played), he produced only three half-notes with no resemblance to the initial intervals (fig. 5). Nor, using a single note, could he write the correct rhythm. Asked to write a C-sharp and shown it on the piano keyboard, he wrote first a treble clef, then a backward note in the bass clef C position, then a misplaced sharp (fig. 6). Asked to copy a simple four-part hymn, he first incorrectly wrote a treble clef, spanning two staves. Starting again, he correctly copied the clefs, and then made frequent errors with note location, duration and bar placement.

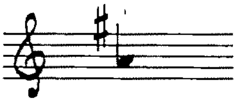

FIG. 6. *Case 2.* Attempt to write a C-sharp.

On November 6 spontaneous speech, naming and auditory comprehension were nearly normal; repetition was still moderately impaired. He wrote well to dictation, and although he wrote few words to describe pictures, what he wrote was correct. He read well aloud and correctly matched written words with both pictures and spoken words.

Music now sounded nearly normal to him. He correctly sang single tones, intervals and well-known tunes, with or without words, after either hearing them or being told their titles. He continued, however, to imitate rhythm badly. Musical writing was still poor. Shown where to put the first note of a heard interval, he misplaced the second most of the time. He could not properly write well-known tunes after hearing them, choosing them himself, or correctly singing them (fig. 7).

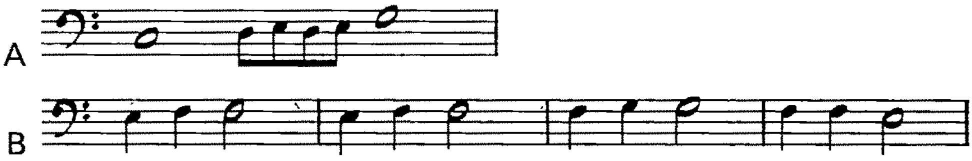

FIG. 7. *Case 2.* A, later attempt to write 'Happy Birthday'. B, attempt to write 'Jingle Bells'.

He wrote simple heard rhythm poorly even when binding it to a single note; it made no difference whether the rhythm was tapped, played as a single note, or bound to a melody (fig. 8). Still error-ridden were his sightreading (singing) of two-note intervals and rhythm, matching of written intervals with what he heard, naming of written single notes, and identification of dynamic symbols, including letter abbreviations.

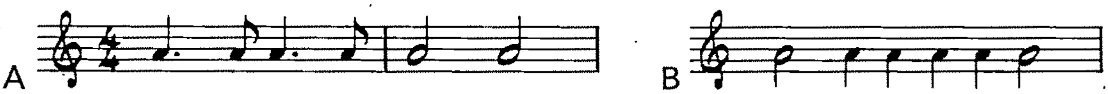

FIG. 8. *Case 2.* Attempt to write rhythm. A, rhythm played for patient on single piano note and then tapped. B, patient's written reproduction of same rhythm.

DISCUSSION

These two aphasic patients had musical dysfunction, yet to compare them with each other and with cases from the literature should discourage one from trying to predict what kind of amusia, if any, might follow a particular brain lesion. Case 1, with transcortical sensory aphasia, had entirely normal musical function except for musical alexia and agraphia, which in turn were greater for pitch than for rhythmic elements. Case 2, with conduction aphasia, had severe expressive (and probably mild receptive) amusia, which affected rhythm more than pitch, plus musical alexia and agraphia in which rhythm and pitch elements were affected with equal severity. Case 1's musical agraphia was less severe than her language agraphia; in Case 2, the reverse was true.

Previous reports cover a spectrum of aphasia without amusia, aphasia with amusia, and amusia without aphasia, and within each category the severity and type of aphasia or amusia varies widely. To appreciate the heterogeneity of each subgroup, including the presence or absence of musical alexia and agraphia, it is useful to review in detail some of these cases, none of whom, however, closely resembles either of the present patients.

Aphasia without Amusia

The first report of aphasia with relatively preserved musical ability was probably Dalin's (1745). A man with right hemiparesis and speech limited to the word 'yes' could sing hymns learned before his illness. To get started, however, he had to hear someone else singing the same song. He could also 'recite certain prayers without singing, but with a certain rhythm and in a high-pitched shouting tone'. Similar nineteenth-century reports were summarized by Edgren (1895), who found that aphasia and normal musical function were as common as aphasia plus amusia. Jackson (1871) described two children with non-fluent aphasia; one could sing with words; the other could sing only without them. Henschen (1925), citing 89 cases of aphasia and preserved musical function, found that appreciation of pitch might be intact with altered rhythmic sense, or *vice versa*. Critchley (1953/1966) described a patient with jargon aphasia, due to left parieto-temporal glioma, who was able to conduct his own orchestra.

A 47-year-old right-handed man (Smith, 1966), globally aphasic following left hemispherectomy, gradually recovered considerable auditory comprehension, although his speech remained severely limited. He was able to sing familiar songs 'with little hesitation and few errors in articulation'. Similarly preserved singing followed left hemispherectomy (Gott, 1973) in a right-handed 14-year-old whose spontaneous speech was 'limited as a rule to single words or short phrases'.

A woman who survived carbon monoxide poisoning (Segarra and Quadfasel, 1961; Geschwind, Quadfasel and Segarra, 1968) had spontaneous speech limited to a few recurrent utterances (e.g. 'Hi, Daddy'), echolalia, palilalia and no apparent language comprehension. She could sing the words and music of familiar songs and of new material taught to her. Serial speech was adequate for a few digits and months, and she could say rhymes but not random words in unison with the examiner. At autopsy there was widespread destruction of frontal, parietal and temporal lobes (including both temporal tips), but preservation of peri-opercular regions. The authors considered the case an example of mixed transcortical aphasia (Goldstein, 1917), due to 'isolation of the speech area', and correlated the pathology with her ability to repeat rather than with musical function *per se*.

Yamadori, Osumi, Masuhara and Okubo (1977) found that 21 of 24 Broca's aphasics sang satisfactorily, six excellently. Two produced poor melody and one was unable to form a melody at all. Six of the 21 who sang well could not produce words with the melody and 3 contaminated the words with literal paraphasias. Eight who could sing required a few notes by the examiner to get started. Ability to sing, with or without words, did not correlate with severity of aphasia.

Preserved musical function in aphasics has included musical reading and writing. Jackson (1871) cited a patient of Trousseau's, 'completely aphasic', including alexia and agraphia, who 'could note down a musical phrase sung in his presence'.

The Russian composer Shebalin, despite severe Wernicke's aphasia, with alexia and agraphia (Luria, Tsvetkova and Futer, 1965), continued musical composition '. . . which other musicians considered to be up to standard', including songs, quartets, choruses and a symphony. At autopsy there was 'massive red softening of the left hemisphere of the brain in the temporal and inferior parietal regions'. Luria *et al.* concluded that '. . . phonematic and musical (prosodic) organization of acoustic perception and memory are included in different systems, and have as their basis different cortical structures.' A similar patient (Blau and Henson, 1977) had severely impaired comprehension of spoken and written speech, yet could read music and play the piano properly with his left hand.

A professional pianist (Assal, 1973) with Wernicke's aphasia, including moderately severe alexia and agraphia, continued to play the piano publicly. Not only could he play melodies sung to him, whether or not he had heard them before, reproduce heard chords, and recognize dynamics, instruments and intentional errors, but he could read a score nearly correctly and could write and compose music.

Aphasia plus Amusia

A number of nineteenth-century workers reported amusia in aphasics (Edgren, 1895). Although usually neither language nor musical dysfunction were described in detail, it was apparent that amusia could be expressive, receptive, or mixed, and that it was sometimes of uncertain type. A left-handed aphasic with a right hemispheric lesion (Finkelnburg, 1870) could play heard melodies on the violin but not on the piano.

A patient with mild anomia (Pötzl and Uiberall, 1937) heard music as dissonant and voices, including his own, as too high-pitched; he could neither sing nor reproduce rhythmic patterns. At autopsy the auditory cortices were bilaterally damaged. A professional singer with absolute pitch (Jellineck, 1956) had anomic aphasia with mild alexia and agraphia. Her major musical disability consisted of difficulty recognizing melodies she had once sung unless the words were added. A patient with Wernicke's aphasia (Kleist, 1962) was unable to recognize or play familiar melodies although he could still appreciate pitches and intervals, tuning his zither precisely and reproducing chords properly. At autopsy there was infarction of the left anterior second and posterior first temporal convolutions, extending into the supramarginal gyrus. Two aphasic patients (Dorgeuille, 1966) following left anterior temporal lobe surgery had difficulty discriminating tone and, in one, timbre. A third patient, with a more posterior left temporal lobe lesion, had difficulty recognizing tonal sequences.

Receptive amusia has accompanied both auditory agnosia and pure word deafness. A woman unable to distinguish speech from music following a lesion in the left superior temporal transverse gyri (Heschl's and adjacent) could, however, sing songs after reading their titles (Schuster and Taterka, 1926). A man with word deafness but nearly normal speech (Ziegler, 1952) could not recognize melodies, and although able to tell which of two or three notes was higher, could not reproduce intervals. He imitated heard rhythms but not dynamics. A patient who heard speech, including his own, as an 'undifferentiated mass of sounds without structure or rhythm' and could not repeat spoken words (Klein and Harper, 1956) could none the less recognize people's voices and regional accents and identify other sounds and melodies. He could not, however, reproduce melodies correctly.

After excision of a right frontal glioma, a right-handed man (Botez and Wertheim, 1959) had left hemiparesis and aphasia consisting of dysarthria and altered prosody on spontaneous speech and repetition, mildly impaired speech comprehension, paraphasias on reading aloud and paragraphias. Although lacking musical training, he had played the accordion and sung in a dance band. A year after operation language function was nearly normal except for dysprosody and tachyphemy, yet he still sang 'wrong' and could not play his instrument. On formal testing he correctly sang notes sung to him, but hearing them played on his accordion, he sang them a fourth too high or too low. He was aware of his errors but could not correct them. Imitation of rhythm was poor, improving when it was 'bound' to a melody. He sang well-known tunes poorly with wrong tones, poor stress, inappropriate staccato and tremulo, and inability to do accelerando *vs* ritardando or crescendo *vs* decrescendo. Attempts to learn new songs failed; rhythm was especially poor. He could not play his accordion, although he held his hands correctly. As the authors conceded, cerebral language dominance was uncertain in this patient. If bihemispheric language representation is likely in dextrals with 'crossed aphasia' (Brown and Hécaen, 1976), the question of 'musical dominance' in such patients becomes even more problematical than in conventional right-handers. Predominantly motor amusia was described in another dextral with crossed aphasia by Barraquer-Bordas, Mendilaharsu, Peres-Serra, Acevedo de Mendilaharsu and Grau-Veciana (1963).

In cases of aphasia plus amusia, musical reading and writing may be either spared or affected. Proust (1866) reported an aphasic patient who could recognize, sing, play and write music, but could not read it. An aphasic music teacher (Fischer, 1867) recognized melodies and rhythmic patterns and could play tunes on the violin but could neither read nor write music, nor play or sing tunes sung to him. A woman (Proust, 1872) with 'a smattering' of musical knowledge had conduction aphasia with agraphia but normal reading comprehension; she could read notes, play scales, and recognize tunes, but could not hum them. A 'completely aphasic' musician (Proust, 1872), unable to speak or write, was also unable to hum, yet she recognized melodies, read music and composed. Dejerine's (1892) patient with pure alexia also lost the ability to read music; speech, writing and singing were normal.

A piano teacher (Souques and Baruk, 1926, 1930) sustained infarction of the left superior posterior temporal lobe, causing jargon aphasia with severely impaired speech comprehension, reading and writing. She could play, spontaneously, a simple 'air de danse' on the piano, but no other piece. Scales were played properly after demonstration by the examiner, and she imitated rhythm well but although she could play scales in thirds, she could not play them in sixths or ninths. She could not play, copying the examiner, simple tunes, although she sometimes reproduced the correct rhythm with wrong notes. She recognized deliberate errors in scales. In contrast to her inability to play what she heard, she played from score perfectly a Clementi sonatina. A prelude from Bach's *Well-tempered Klavier* was performed slowly, as by a novice. She copied music well, although transposing with difficulty, and she wrote correctly music she heard.

Each of Ustvedt's (1937) 19 patients with left hemispheric stroke, most of whom were aphasic, noted less emotional involvement with music afterward. Uniformly impaired were appreciation of measure and recognition of short melodic-rhythmic figures; appreciation of pitch, volume, and timbre was intact. Some had difficulty singing; others sang well, with or without words. In the few who had been able to read music pre-morbidly, musical alexia paralleled or was worse than language alexia.

Maurice Ravel had Wernicke's aphasia, alexia, agraphia and ideomotor apraxia (Alajouanine, 1948); a definite ætiology was never established. 'Memory, judgement, affectivity, (and) æsthetic taste' were said to be intact, as was 'musical thinking': he recognized melodies and errors of rhythm and pitch, including a badly tuned piano. He could not, however, play the piano or sing properly, either spontaneously, by imitation, or from score, nor could he name, play, or sing written notes. He wrote music poorly, although better than he wrote words; copying music was 'almost impossible'. Alajouanine did not determine to what degree Ravel's difficulties with musical expression, reading and writing involved rhythm, pitch, interval, or melody, but simply observed that, although he could 'still listen to music, attend a concert, and express criticism on it or describe the musical pleasure he felt', he never again was able to compose the pieces he heard 'in his head'.

A singer-guitarist after left frontal lobe surgery (Jellineck, 1956) had mixed aphasia, including alexia and agraphia, as well as mixed amusia. Singing was wrong in pitch and rhythm, worsening if words were added, and scales and pure phrases were more difficult than extended tunes. He did not recognize his errors. He could immediately repeat melodies, but could not later recognize them and often did not recognize well-known melodies. Musical alexia was total, and worse than reading language; he could not even orientate himself on the page, tell if a note was higher or lower than another, or identify a chord.

A professional violinist with absolute pitch had mild Wernicke's aphasia and right hemiparesis following a stroke (Wertheim and Botez, 1961). There were paraphasias on spontaneous speech, naming and repetition, decreased comprehension for complex commands, paralexias on reading aloud and mild agraphia. Reading comprehension was intact. Amusia was said to be 'receptive' because of difficulty naming intervals, pitches, and rhythmic patterns and inability to name familiar melodies played on the piano after correctly identifying them when they were sung. Some of his other difficulties, however, could have been either receptive or expressive, for example, failure to imitate heard rhythm or to sing a melody previously unknown to him, and some were probably expressive, for instance, singing familiar songs with frequent intonational errors. He copied music correctly, but writing music both spontaneously and to dictation was poor; rhythm was better than placement of notes. He named most notes correctly in the treble clef but had great difficulty with the bass and viola clefs; he could not sing solfeggio simple tunes written on any clef. A problem with this case is that, in addition to the difficulty in defining many components of his amusia as either 'expressive' or 'receptive', it is not clear whether the anomia and decreased speech comprehension distorted the results of musical testing.

An orchestral conductor and composer (Critchley, 1970) was unable to play the piano or write music properly while aphasic, although he said '. . . I have the music in me'. Following removal of a left parietal meningioma, speech and ability to compose seemed to improve in parallel.

Amusia without Aphasia

Not surprisingly, cases of amusia without aphasia have been reported infrequently. Edgren (1895) collected 5 cases from the literature, in contrast to 23 with amusia plus aphasia. There have been several accounts of right hemispheric damage with inability to sing or to whistle but with preserved language function and melody recognition; such patients have had either frontal (Mann, 1898) or temporal (Brain, 1941) lobe injury, or even hemispherectomy (Damasio, Lima and Damasio, 1975). Gordon and Bogen (1974) found, following right carotid amobarbital injection to right-handed subjects, impaired singing ability; pitch was more affected than rhythm, but patients had a general tonal sense, tried to correct errors and could recognize songs sung to them. Speech was rather dysarthric, but had normal prosody and phonetic stress.

Difficulty with musical perception has been described. Kohl and Tschabitscher (1953) and Pittrich (1956) reported inability to recognize musical sounds following right hemispheric lesions, and Pötzl (1939) reported difficulty appreciating rhythm. Following right temporal lobe surgery, a man (Jellineck, 1956) reported that music sounded 'out of tune'. He found it easier to imitate melodies sung by male than by female voices; chords, however, were better recognized when high-pitched. Rhythm was normally appreciated, but rhythmic changes gave him a sense of tonal change as well. A woman with a right thalamic tumour (Roeser and Daly, 1974) experienced 'gross distortion of music perception in her left ear'. A man unable to recognize any non-verbal sounds (Spreen, Benton and Fincham, 1965) was poor at pitch identification, yet could comprehend speech. At autopsy there was infarction of the right frontal, parietal and temporal lobes and insula.

Milner (1962) gave the Seashore Test of musical abilities (which measures discrimination of pitch, loudness, rhythm, duration, timbre and tonal memory) to 27 left speech-dominant patients before and after either right or left temporal lobectomy. Whereas there was no loss of musical ability after left lobectomy, deterioration followed right lobectomy, slight for pitch and rhythm, marked for timbre and tonal memory. There was no difference whether or not Heschl's gyrus was removed. Shankweiler (1966) found that whereas melody recognition deteriorated after right temporal lobectomy, pure frequency discrimination did not.

Musical reading and writing have seldom been tested in patients with amusia but not aphasia. A professional trombonist and music copier, seen by Charcot (Souques and Baruk, 1930), suddenly lost the ability to copy music or to play his trombone properly, yet he appreciated music and could read it, singing it mentally. There was no weakness or other apraxia and language function, including reading and writing, was normal. The site of pathology was not determined. Jossmann's (1927) patient, following right carotid ligation and left hemiparesis without aphasia, could neither sing, whistle tunes, nor read music, but recognized pitch and his own errors. A trumpeter, after head injury (Dorgeuille, 1966), had difficulty writing heard rhythmic patterns; language and musical function were otherwise normal.

The Present Patients

The varieties of amusia, including musical alexia and agraphia, are thus not predicted by the presence or absence of aphasia, and there is considerable heterogeneity among those cases of aphasia with normal musical function, including musical reading and writing (Jackson, 1871; Luria, Tsvetkova and Futer, 1965; Assal, 1973; Blau and Henson, 1977), aphasia with amusia, including musical alexia and agraphia (Fischer, 1867; Ustvedt, 1937; Alajouanine, 1948; Jellineck, 1956; Wertheim and Botez, 1961), and aphasia with amusia but preserved musical reading and writing (Proust, 1872; Souques and Baruk, 1926, 1930).

The present Case 1, with transcortical sensory aphasia and normal musical function except for musical alexia and agraphia, appears to have no well-studied counterpart in the literature. Proust's (1866) patient, while unable to read music, could write it. Dejerine's (1892) patient was unable to read music as part of a pure alexia syndrome. How much Case 2, with conduction aphasia, resembles previously reported patients is uncertain, as details of both language assessment and musical reading and writing have usually been absent. Proust's (1872) patient with conduction aphasia could not hum tunes, but could play scales and read notes; she apparently had never written music. Jellineck's (1956) patient had mixed aphasia and more severe musical alexia. Wertheim and Botez's (1961) patient had rather similar aphasia, although the relative severity of comprehension and repetition is unclear, and reading comprehension and writing were better preserved than in Case 1's earliest testing. As with Case 2, there were abnormalities of musical function which could have been either receptive or expressive. In contrast to our case, Wertheim and Botez's patient copied music well and wrote rhythm better than he designated pitch. Anomia and expressive (singing) amusia leave the degree of his musical alexia uncertain, and many components of musical reading and writing were not tested.

Musical Reading and Writing

Musical reading and writing involve 'skills commonly believed to be language-specific' (Henson, 1977*b*). Sloboda (1976), comparing musically literate and illiterate subjects, found that the musically sophisticated, when analysing written note sequences, appeared to use neither visual (that is, spatial), naming, nor pitch codes but rather to code 'relations between the notes rather than the notes themselves'. Similar processing has been suggested to underlie the reading of language (Kolers, 1972). Musical reading and writing, however, involve more heterogeneous symbols than ordinary reading and writing of words. There are real words, often abbreviated (allegro, largo, DC, *pp*, *f*, etc.); notes whose pitch is designated by letters (A, B, C, etc.) but represented spatially, and whose duration is indicated by appearance (minim, crotchet, quaver, etc.); metre, expressed as numerical fractions and dependent upon placement of bars; and purely musical symbols for pitch alteration and key signature (sharps, flats, naturals), pauses (rest), tonal prolongation (fermata), pitch calibration (clef), crescendo or decrescendo, staccato, legato and repeat. Both simultaneous and sequential events are indicated.

It was therefore of interest to determine whether those aspects of musical notation closest to verbal language or most dependent upon temporal (sequential) processing were maximally impaired in our aphasic patients. Such was not the case. In fact, the first patient suggested an opposite dissociation. Her maximal difficulty with reading music was with note placement (pitch designation); she could not read single notes, two note intervals or chords properly, but knew whether the second of two notes was higher or lower. That this difficulty did not reflect inability to read notes as letters is suggested by the fact that she named written notes and intervals better than she sang or played them. She was considerably more adept at reading the kind of note present, key and time signatures, accidentals, dynamic and agogical symbols, word abbreviations and significantly, from the standpoint of sequential processing, pure rhythm. Writing music led to errors of both pitch and rhythm, whether done alone or together. Her greater difficulty reading and writing in the bass clef paralleled reports of others (Wertheim and Botez, 1961) as well as the experience of beginning musicians. At her second examination reading alexia and musical alexia-agraphia had all improved more than language agraphia, and there was particular improvement in writing rhythm.

Case 2 showed no dissociation between temporal and non-temporal or verbal and non-verbal elements in his musical alexia and agraphia (or, for that matter, early in his expressive and receptive amusia, although later he could imitate pitch and interval better than rhythm). Like Case 1 he named written notes better than he sang, played or wrote them. Unlike Case 1, his musical alexia and agraphia remained severe when his language alexia and agraphia had improved considerably, and he had more difficulty recognizing musical dynamic abbreviation (*p*, *pp*, *f*, *ff*) than in reading letters, words or sentences.

A Japanese patient with transcortical sensory aphasia (Sasanuma and Monei, 1975) could not comprehend written kanji (Chinese ideogrammatic) characters yet understood kana (phonetic) characters and wrote kanji with more difficulty than kana. Conversely, preservation of kanji relative to kana reading has been reported in anomic aphasia (Yamadori, 1975). No such dissociation between kinds of musical symbol occurred with either Case 1 or Case 2.

Like a patient with better repetition than auditory comprehension (Albert, Yamadori, Gardner and Howes, 1973), Case 1 had severe disability comprehending written words or sentences and spelled words, yet successfully matched written words with appropriate pictures, suggesting preservation of 'semantic understanding' of written words. There was no corresponding ability to match written musical notes or intervals with what she heard played or what was spoken to her. Non-pitch musical alexia was too mild for such dissociation to be testable.

As noted, it seems unlikely that letter coding was the main reason for these patients' difficulty reading and writing pitch; it cannot, however, be dismissed as a contributing factor. Experienced musicians do not usually name individual notes or chords as they read them (Henson, 1977*b*), but beginners do. Several reported patients with aphasia but preserved musical reading and writing were older or more musically experienced than our patients (Souques and Baruk, 1926; Luria, Tsvetkova and Futer, 1965; Assal, 1973). On the other hand, so were some with aphasia, amusia and musical alexia-agraphia (Alajouanine, 1948; Jellineck, 1956; Wertheim and Botez, 1961).

Singing and Repetition

When Case 1's aphasia was still moderately severe, she could sing nearly flawlessly, in five languages, songs learned since her illness. Reports of aphasics who sing better than they speak have been mostly concerned with Broca's or otherwise non-fluent speech (Yamadori *et al.*, 1977; Geschwind *et al.*, 1968) and have included those who could sing with words (Jackson, 1871; Ustvedt, 1937; Smith, 1966; Gott, 1973; Geschwind *et al.*, 1968; Heilman, Tucker and Valentstein, 1976; Yamadori *et al.*, 1977) and those who could not (Jackson, 1871; Head, 1926/1963; Jellineck, 1956; Yamadori *et al.*, 1977). The ability to sing words which could not be spoken has been attributed to the factor of automaticity. Ustvedt (1937) cited the same phenomenon in parkinsonians and stutterers. Goldstein (1927) suggested that singing would be preserved in an aphasic to the degree that '. . . it is an activity closely connected to the patient's affective life. Under such conditions the song is not representative speech, but a "series speech" performance expressive of feeling, like a prayer.' More mechanistically, Bogen (1969) suggested that the addition of words to song might lead to transcallosal inhibition of the right hemisphere by the left.

Whether Case 1's ability to sing with words was related to her relatively preserved repetition, as with the cases of Geschwind *et al.* (1968) and of Heilman *et al.* (1976), and whether Case 2's inability to sing, with or without words, was related to his particular difficulty with repetition, is conjectural. Case 1 sang well in English and made infrequent paraphasic errors in foreign languages. Henson (1977*c*) stated 'There is no apparent record of any professional vocalist who was able to perform acceptably with permanent dysphasia'. This statement would apply to Case 1 as far as non-English singing is concerned, yet she has been able to pursue a singing career within the limits of popular songs in her own language.

It is also speculative whether Case 2's particular difficulty in repetition was related to his disability with written and imitated rhythm. Musical function was not discussed in a recent review of conduction aphasia (Benson, Sheremata, Bouchard, Segarra, Price and Geschwind, 1973). It is difficult to relate his repetition deficit to his greater difficulty, compared to Case 1, with non-pitch written symbols, either ideogrammatic, numerical or word abbreviations, but it is of interest that whereas his alexia-agraphia for language became much milder than Case 1's, his musical alexia-agraphia for these types of symbols was much more severe. Unlike Case 1 he had difficulty in matching written words with pictures; in addition, like her, he could not match heard intervals with a read score. His musical alexia-agraphia remained severe when music sounded normal to him and he could sing heard notes, intervals and songs, yet was still unable to imitate simple rhythms, whether bound to melody or not.

Experimental Studies

Attempts, using dichotic or reaction-time techniques, to determine hemispheric superiority for components of music have yielded conflicting results. Kimura (1964), playing fragments of different baroque and classical melodies simultaneously into the ears of normal subjects, found the left ear, and therefore presumably the right hemisphere, superior in melody recognition. King and Kimura (1972) demonstrated left ear superiority for non-verbal human voice sounds as well (for example, laughing, crying, coughing). Schuloff and Goodglass (1969) showed, in normals, left ear superiority for tonal sequences, right ear superiority for spoken digits, and no difference for simple clicks. For pure tone recognition Kallman and Corballis (1975) found left ear superiority, Haydon and Spellacy (1973) right ear superiority, and Nachshon (1973) no difference. Kallman and Corballis (1975) found left ear superiority for timbre, and Robinson and Solomon (1974) right ear superiority for rhythm, but Spellacy (1970) detected no difference for either. Gordon (1970) found left ear superiority for chord recognition but no difference for melodies. Spellacy (1970) and Spreen, Spellacy and Reid (1970) believed that asymmetry for music recognition was influenced by duration of the interstimulus interval. Halperin, Nachshon and Carmon (1973), using dichotic sets of three tones, found that as the number of frequency or duration transitions increased from zero to two, ear superiority shifted from left to right.

As noted, musical understanding involves both sequential-analytic and simultaneous-gestalt processing and so, more than language, might be expected to require co-operation between the 'propositional' left hemisphere and the 'appositional' right. Speech itself is, of course, not wholly a left hemispheric activity (Larsen, Skinhøj and Lassen, 1978). It is hardly surprising, therefore, that those studies which have attempted to isolate temporal and non-temporal aspects of musical ability have not consistently placed them in either the left or right hemisphere (Wyke, 1977). Moreover, people listen to or perform music differently. Werner (1948) observed 'Musically experienced listeners have learned to perceive a melody as an articulated set of relations among components rather than as a whole'. Consistent with this idea, Bever and Chiarello (1974) found that, whereas musically naïve listeners recognized melodies better with the left ear, sophisticated listeners did better with the right. The authors noted that Gordon (1970) had used college students of probably intermediate sophistication, perhaps explaining their non-lateralization of melody recognition. On the other hand, Cook (1973) found left ear superiority for melody recognition in sophisticated listeners. Oscar-Berman, Blumstein and DeLuca (1974), using bilateral simultaneous tachistoscopy, demonstrated that musically sophisticated subjects were more likely than those musically naïve to use both hemispheres in the analysis of musical symbols.

If Case 1's musical sophistication had led, pre-operatively, to left hemispheric musical dominance, with post-operative return to right hemispheric musical processing, such a change was not reflected in her non-lexical musical ability, subjectively or objectively. Left hemispheric destruction was massive and the anterior temporal lobe was amputated. Musical sophistication, with prominent left hemispheric participation in analysing musical symbols, could have contributed to musical alexia and agraphia, but would be at variance with cases from the literature of preserved musical reading and writing in aphasic professional musicians and composers (Souques and Baruk, 1926; Luria *et al.*, 1965; Assal, 1973; Blau and Henson, 1977).

Case 2, although a musically literate professional musician, was less sophisticated than Case 1, and so his musical abilities might be expected to be less dependent upon the left hemisphere. Moreover, his lesion was far smaller than Case 1's and, by computerized tomography, occupied an area shared by Case 1's lesion. Yet, in contrast to her, he did have expressive and probably receptive amusia, and, whereas his aphasia was milder than hers, his musical alexia-agraphia was more severe.

Conclusion

These two cases thus do not clarify the question of music's relation to speech, language and hemispheric function; rather, consistent with previous literature, they illustrate the complexity of the problem and the prematurity of defining as propositional or appositional either music, its components, or the kind of processing employed by each hemisphere. Chomsky (1972), stressing the inadequacy of present concepts of language and the need to study it in abstract, not physical, terms, stated 'We can only leave open for the future the question of how these abstract structures and processes are realized or accounted for in some concrete terms, conceivably in terms that are not within the range of physical processes as presently understood—a conclusion that, if correct, should surprise no one.' The same can be said about music.

SUMMARY

Two aphasic right-handed professional musicians with left hemispheric lesions had disturbed musical function, especially musical alexia and agraphia. In Case 1 aphasia was of transcortical sensory type, with severe agraphia and decreased comprehension of written words, although she could match them with pictures. Except for reading and writing, musical ability was normal; she could sing in five languages. Musical alexia and agraphia affected pitch symbols more than rhythm. Case 2 had conduction aphasia and severe expressive amusia, especially for rhythm. Although his language alexia and agraphia were milder than Case 1's, his musical alexia and agraphia were more severe, affecting rhythm as much as pitch. In neither patient were those aspects of musical notation either closest to verbal language or most dependent upon temporal (sequential) processing maximally impaired.

These cases are consistent with the literature in suggesting that the presence or absence of aphasia or of right or left hemispheric damage fails to predict the presence, type, or severity of amusia, including musical alexia and agraphia. The popular notion that receptive amusia follows lesions of the language-dominant temporal lobe, whereas expressive amusia follows non-dominant frontal lobe damage, is an over-simplification, as is the view that increasing musical sophistication causes a shift of musical processing from the right hemisphere to the left.

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ANTICIPATORY POSTURAL REFLEXES IN PARKINSON'S DISEASE AND OTHER AKINETIC-RIGID SYNDROMES AND IN CEREBELLAR ATAXIA

by M. M. TRAUB, J. C. ROTHWELL *and* C. D. MARSDEN

(*From the University Department of Neurology, Institute of Psychiatry and King's College Hospital Medical School, London SE5 8AZ*)

ANTICIPATORY postural responses in normal human subjects have been described by Marsden, Merton and Morton (1978). If the arm meets with an unexpected perturbation while executing a simple manual tracking task, early automatic electromyographic (EMG) responses can be detected in distant muscles concerned with posture. These reflex responses are in such a direction so as to compensate for any bodily movements caused by the disturbance. For example, in the experiment described by Marsden *et al.* (1978) the task was to flex the elbow of one arm at a constant rate against a load attached to the wrist whilst the kneeling subject steadied himself by holding a table top with the contralateral arm. When the load was unexpectedly altered, compensatory EMG responses were seen in biceps and triceps of the supporting arm with a latency of some 55 ms. Since no significant movement of the shoulder of the supporting arm occurred during the latent period of the reflex, it was concluded that the reflex responses in contralateral biceps and triceps were due not to stretching or relaxation of these muscles, but to afferent input from the tracking arm. The critical stimulus to such distant postural reflexes did not arise from the skin of the tracking arm, for anæsthesia of that hand and wrist did not affect them. Marsden *et al.* (1978) concluded that these responses were centrally driven by stimuli produced by movement of the tracking arm activating cerebral mechanisms to cause contraction of appropriate distant postural muscles.

We have examined anticipatory postural responses in the legs of standing human subjects. In normal volunteers pulling against a resistance, if the arm is suddenly jerked forwards a burst of activity can be detected from the calf muscles (triceps suræ) at a latency of about 80 ms: conversely, if the arm is suddenly released, there is a period of silence at a similar latency. We have investigated this postural response in patients with akinetic-rigid and cerebellar syndromes and have compared it to that in age-matched normal subjects. The response is small in most, but not all, patients with Parkinson's disease who have a history and signs of postural instability, and is not affected in equally unsteady patients with progressive supranuclear palsy. Patients with cerebellar syndromes have a normal anticipatory postural response unless they exhibit severe truncal ataxia.

PATIENTS

Akinetic-Rigid Syndromes

Twenty-nine patients with idiopathic Parkinson's disease took part in the experiment. Suitable subjects had to be able to stand unsupported for two minutes and carry out the holding task described below. This excluded patients with severe postural instability (Grade V, Hoehn and Yahr, 1967), severe tremor or marked levodopa-induced dyskinesias. Two patients (R.M. and M.S.) were not on anti-parkinsonian medication at the time of the experiments; the remainder were taking anticholinergics (18 patients) and levodopa (as Sinemet) (27 patients). They were allocated into two groups according to clinical criteria. The 11 patients in the mild group had no history of repeated falls and displayed normal protective reactions if suddenly pushed when standing or tilted sideways on a chair (Grade II). The 18 patients in the moderately severe group all gave a history of at least five falls per month and did not respond protectively to a sudden tilt (Grades III and IV). Both groups of patients were compared with a group of 18 age-matched subjects who were selected from a population of 50 normal controls.

Four patients with progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) were also examined. All demonstrated the typical absence of vertical eye movements associated with akinetic-rigid syndrome without tremor as well as limitations of horizontal gaze.

Patient H.N. had a severe akinetic-rigid syndrome with dementia secondary to cerebrovascular disease. Post-mortem examination (Dr I. Janota) revealed widespread loss of cortical white matter with damage to the putamen and globus pallidus thought to be secondary to long-standing hypertension (Binswanger's disease). There was no abnormality of the midbrain.

Cerebellar Syndromes

Four patients with truncal ataxia were investigated; their clinical features are summarized in Table 3. K.G. and T.B., both with posterior fossa tumours, were also examined after operation. In addition we studied two patients with unilateral limb ataxia without postural instability.

Three epileptic patients with diphenylhydantoin toxicity were examined both when severely ataxic and after recovery. Two normal volunteers were rendered severely ataxic by ingestion of about 200 ml of pure ethanol in orange juice.

The results from a group of 18 young normal volunteers were used for comparison with these various patients with cerebellar ataxia.

Corticomotoneuron Lesions

In order to assess the effect of damage to corticomotoneuron pathways ('pyramidal deficit') on the postural response in triceps suræ to a pull on the arm, four patients with spasticity, brisk tendon jerks and extensor plantar responses (due to hereditary spastic paraplegia in one patient and to cervical myelopathy in the other three) were also studied.

METHODS

Mechanical and Electrical

The details of the recording and computer averaging systems used in our experiments have been described elsewhere (Marsden, Merton and Morton, 1976*a*). Marsden *et al.* (1978) reported anticipatory postural responses in biceps and triceps of kneeling subjects who were supporting themselves by holding on to a table top. We elected to examine similar reflexes in triceps suræ of standing subjects because the kneeling position was intolerable to many patients. The subjects stood with feet together facing a low inertia electric motor (Printed Motors Ltd., type G9M4H) at waist height, the spindle of which rotated a 6 cm diameter wheel. The subject held on to one end of a 20 cm inextensible wire, the other end of which was attached to the edge of the wheel. Rotation of the wheel deflected a beam on an oscilloscope screen by 2 cm for every 10 degrees of rotation, and the subject's task was to keep the beam in the centre of the screen by holding the wire steady (fig. 1). The subject

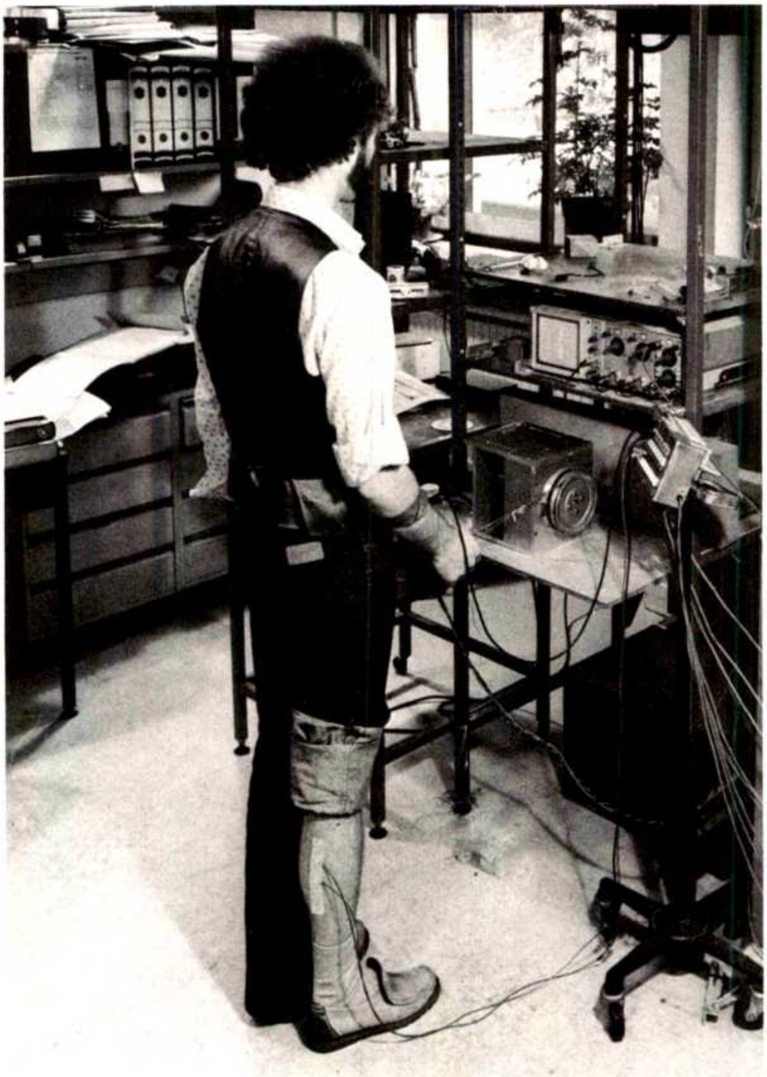

FIG. 1. Apparatus used for eliciting anticipatory postural responses in the legs of standing subjects. A low inertia electric motor is placed at waist height and the subject grasps a loop of wire attached to a pulley fastened to the motor spindle. The angular position of the motor shaft is displayed on an oscilloscope screen above the motor. Also visible are the surface electrodes taped over triceps suræ and an earth plate on the subject's arm.

pulled against a steady load of 3.5 N. At random intervals of between 2 and 5 s the load was abruptly changed to 9 N (a stretch) or to 1.75 N (a release) delivered in random order. The EMG response to these perturbations of the right arm was measured from the ipsilateral triceps suræ using silver-silver chloride surface electrodes, and was recorded for a period of 250 ms starting 50 ms before the perturbation. The EMG was full-wave rectified and integrated, and then averaged by the computer, usually for 32 stretches and 32 releases, together with 32 control runs. The rectified EMG records have been smoothed using a digital 3-point moving average filter for the purposes of illustration. A normal response is shown in fig. 2. The task was performed with little difficulty by all subjects.

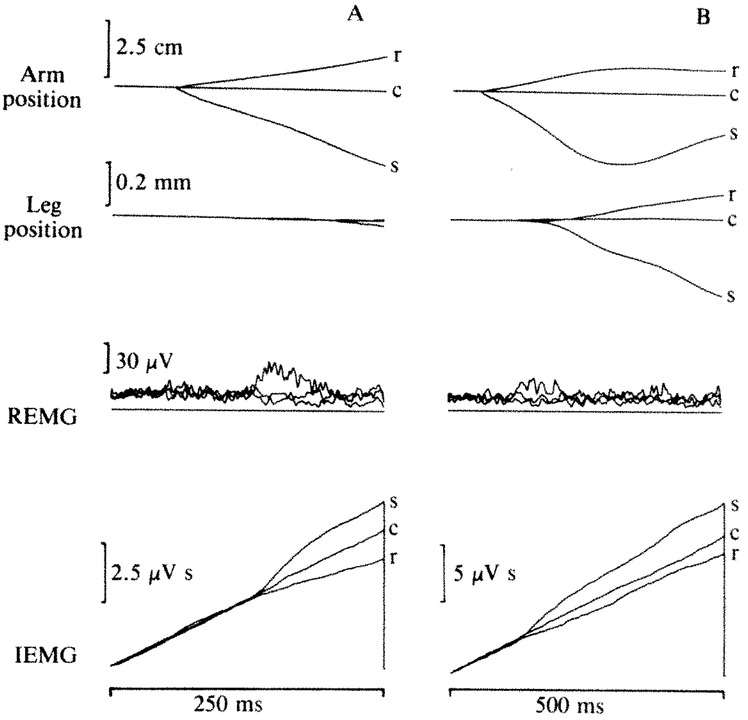

FIG. 2. EMG responses from right triceps suræ in a normal subject following perturbations to the right arm. The traces are, from the top downwards, arm motor position, leg position, rectified EMG (REMG) and integrated rectified EMG (IEMG). B shows another response of the same subject recorded on a longer sweep than A. The perturbation was applied to the arm 50 ms after the start of the record in each case. Each trace is the average of 32 trials. Control (c), stretch (s) and release (r) responses are superimposed.

In some normal subjects the movement of the leg was measured using a very sensitive thin film potentiometer (Bourns 2 inch servo potentiometer). A block of wood was bound over the upper tibia with zinc oxide tape; a light inextensible thread was taken around it to the back of the leg and wound round a 1 cm diameter pulley attached to the spindle of the potentiometer. The end of the thread was then fastened to a weak spring to maintain its tension. Linear movement of the leg thus caused rotation of the potentiometer shaft. Using a micrometer calibration, we found this system to be accurate enough to detect movements of the upper tibia of less than 0.04 mm.

Intravenous Regional Anæsthesia

In one of the authors (M.T.) we examined the effects of intravenous regional anæsthesia on the postural response (Holmes, 1963). A sphygmomanometer cuff was inflated to 180 mm Hg around the thigh and 3 ml of 1 per cent plain lignocaine was injected into a vein on the dorsum of the foot. This produced mild paræsthesiæ of the foot with no apparent reduction in muscle power and completely abolished tendon jerk responses in triceps suræ.

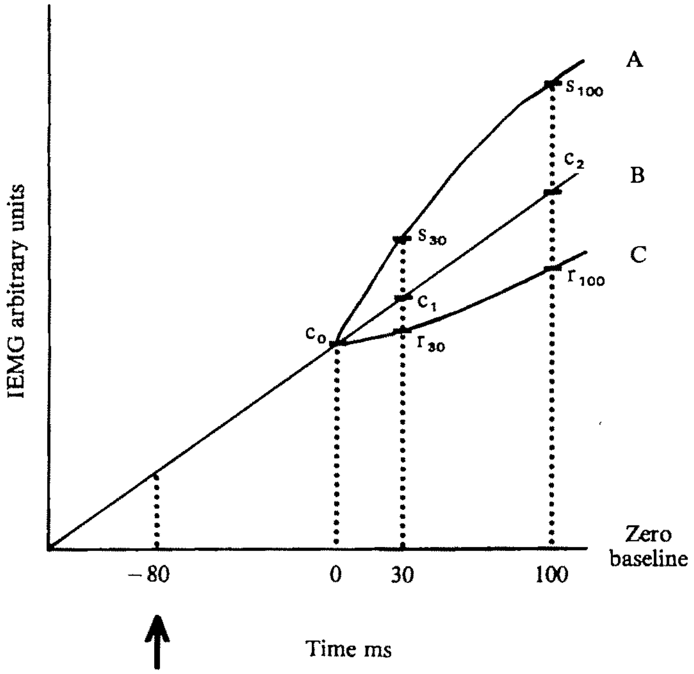

FIG. 3. Method of measuring the integrated EMG response in triceps suræ to a sudden change in the load applied to a subject's arm at the time indicated by the arrow. The EMG response occurs about 80 ms later (at time O). A = response to increased load (a stretch to the arm); B = control; C = response to a decreased load (the arm is released). The size of the responses to stretch (s) or release (r) are measured in arbitrary units from zero baseline with reference to control responses (c) at 30 ms and 100 ms after the onset of the response at time O (*see text* for further details).

Measurement of Data

The size of the anticipatory postural response was estimated from the integrated EMG records separately for stretches and releases 30 ms and 100 ms after the start of the reflex. The slope of the integrated EMG records in control runs varied from subject to subject, because of differences in exact stance, electrode placement and skin resistance. However, as is described in Results, the size of the postural reflex in triceps suræ in any one individual was proportional to the size of the background EMG activity in the period before the perturbation. Thus, the size of the reflex response has been expressed relative to the level of background EMG activity in control runs as shown in fig. 3. The following ratios were computed. S_{30} and S_{100} (relative size of stretch response at 30 ms and 100 ms after the start of the reflex, respectively) and R_{30} and R_{100} (relative size of release response at 30 ms and 100 ms), according to the following formulæ:

$$S_{30}=\frac{s_{30}-c_0}{c_1-c_0} \qquad S_{100}=\frac{s_{100}-c_0}{c_2-c_0}$$

$$R_{30}=\frac{r_{30}-c_0}{c_1-c_0} \qquad R_{100}=\frac{r_{100}-c_0}{c_2-c_0}$$

Statistics

Two-sided Student's t test was used to compare the latencies of the responses, which were distributed normally. Non-parametric methods were used to analyse the size of the reflex which was not normally distributed in any of the groups. The distribution of the size of the reflex was the same in the group of normal subjects and patients with mild Parkinson's disease, so the Mann Whitney U test was used to compare their mean values. The distribution of the size of the reflex in the moderately disabled group was different from that in normal controls, so the Kolmogorov-Smirnov test was used to compare their mean values.

RESULTS

Normal Subjects

The averaged response of a single normal subject is shown in fig. 2A. Fig. 2B shows the same subject's response on a longer time scale so that the leg movement is more clearly visible. The responses in triceps suræ began 80 ms after the perturbation was applied to the arm, yet movement of the leg was not apparent until about 150 ms. The response is in such a direction as to compensate for body sway caused by the movement of the arm. When the arm is pulled forwards, triceps suræ activity increases and reduces the forward sway of the body; when the arm is released there is a corresponding decline in muscle activity. Responses similar to these were found in all 50 normal subjects. Age and sex did not affect their size or latency.

To confirm that these responses were not driven by local stretch of the calf muscles we used the technique of intravenous regional anæsthesia (*see* Methods). Fig. 4 shows that this procedure had no effect on the anticipatory postural response although it virtually abolished the monosynaptic tendon reflex.

Gain Control

The size of the reflex response in triceps suræ to arm pull or release was an approximately constant fraction of the background level of EMG activity. In fig. 5 a normal subject produced different basal levels of activity in triceps suræ by varying the degree to which his body leaned forward. The same size of perturbations were given to the arm in each case and the integrated EMG records from triceps suræ have been scaled to have the same initial slopes (note the different calibration markers). It can be seen that the response is a constant proportion of the basal activity over a range of 4:1. This phenomenon has made it possible to normalize all our results to the basal EMG activity for purposes of comparison between subjects. A similar phenomenon has been noted when a muscle is stretched or released directly as in the human long thumb flexor (Marsden *et al.*, 1976*a*).

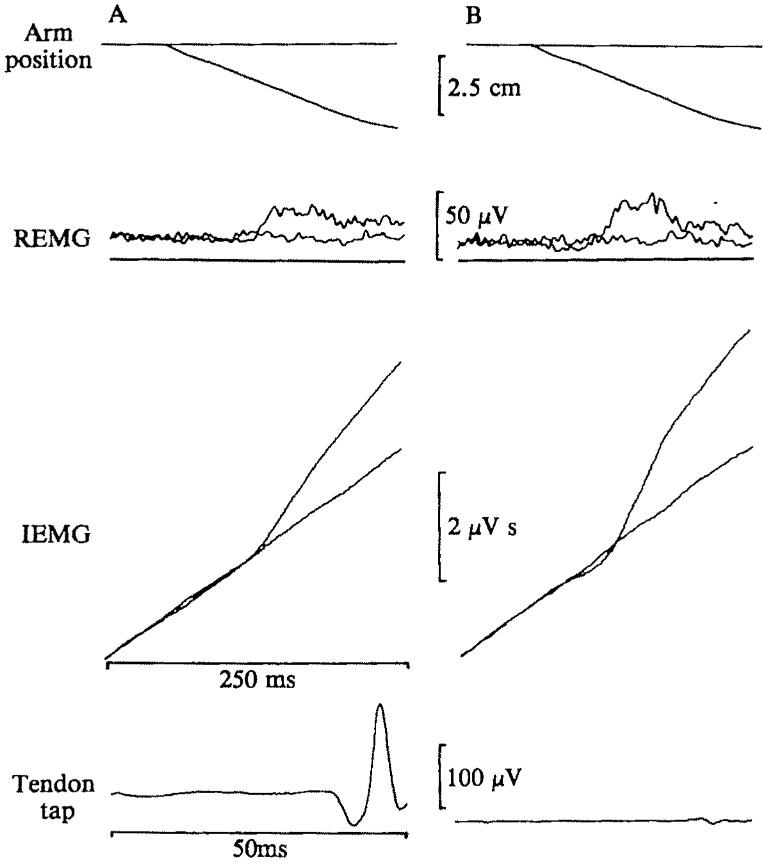

FIG. 4. Effect of intravenous regional local anæsthesia on the anticipatory postural response in triceps suræ and on the Achilles tendon jerk. The top three traces are the average of 32 trials each and are plotted on a 250 ms time sweep to illustrate the anticipatory postural response to a pull on the ipsilateral arm. They show arm position, rectified EMG (REMG) and integrated EMG (IEMG) from triceps suræ. The bottom trace shows the unrectified EMG response to a single tendon tap and is plotted on a 50 ms time sweep which was triggered by a microswitch in the tendon hammer on impact. In A the responses are ilustrated in the intact limb; in B after intravenous injection of local anæsthetic into the dorsum of the foot.

Parkinson's Disease

An averaged response from a moderately severely affected patient with Parkinson's disease is illustrated in fig. 6. Although the change in motor torque produces an arm movement very similar to that in the normal subject illustrated (fig. 2) there is almost no change in the level of EMG activity in triceps suræ; only a small, brief silencing is seen in this patient with Parkinson's disease at about 100 ms after release. The S_{30} and S_{100} values in this patient, measured as described in Methods, were both 1.0, and the R_{30} and R_{100} values were 0.98 and 0.95 respectively.

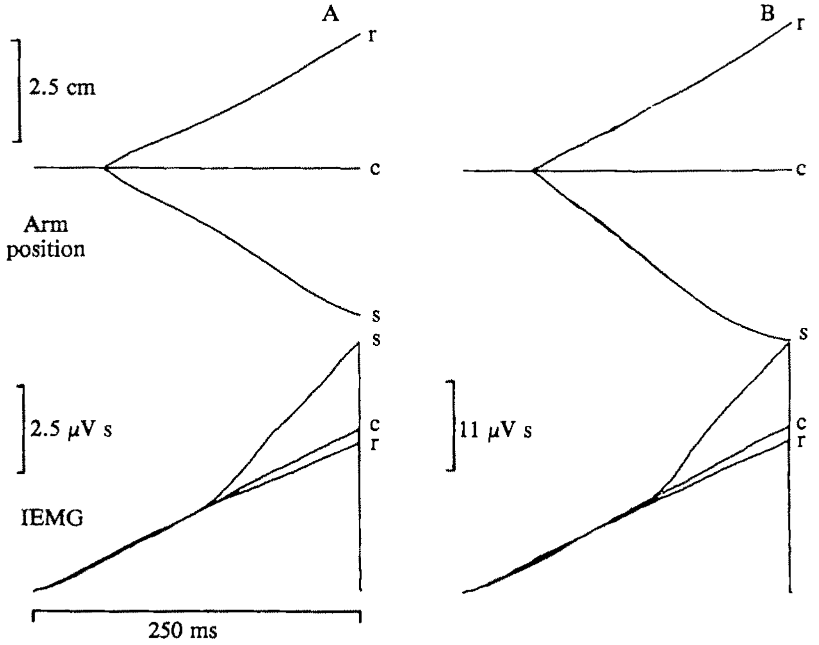

FIG. 5. Change of size of EMG response in triceps suræ to stretch (s) or release (r) of the arm with change in background EMG activity. Upper traces show arm motor position, lower traces illustrate integrated rectified EMG (IEMG) from triceps suræ. In A the subject stood in a normal relaxed stance, in B he leaned slightly forward to increase basal levels of muscle activity in triceps suræ. The integrated EMGs have been scaled to have approximately equal control slopes in A and B (note the different calibration markers). Each trace is the average of 40 trials. The same perturbations were given to the arm in both A and B.

In figs. 7 and 8 the S_{30} and S_{100} and the R_{30} and R_{100} values for all normal subjects and patients with Parkinson's disease are ilustrated. The mean value for each ratio (indicated by the heavy horizontal bar) is close to 1.0 in the moderately affected patients with Parkinson's disease. Patients with mild Parkinson's disease had larger mean responses, but they were still smaller than those obtained in the normal controls.

Statistical comparisons have been made in Table 1 between the sizes of the responses to stretch and release together with the estimated latencies of the response in the patient groups and the age-matched normal subjects. The patients with Parkinson's disease as a whole, combining the data from moderately severe and mild groups, had smaller stretch and release responses measured at either

30 ms or 100 ms than the control group. The latency of the responses in those patients who had a measurable reflex, was no different to that in control subjects.

The mean sizes of the responses to stretch and release in the mildly affected patients who had no history of falls was only slightly smaller than those in normal subjects. The greatest differences were seen in the patients with moderately severe Parkinson's disease, in whom there was on average virtually no response to arm release, and only a brief small response to stretch.

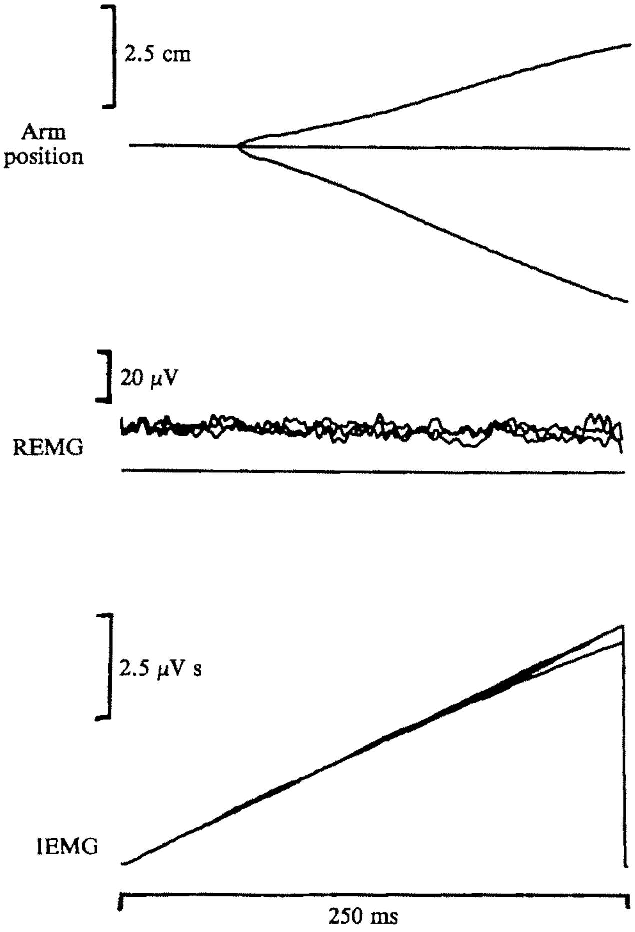

FIG. 6. Responses from a typically moderately severe patient with Parkinson's disease. The traces are, from top downwards, arm motor position, rectified EMG (REMG) and integrated EMG (IEMG) from triceps suræ.

There was no difference in the size of the response to stretch and release in the two untreated patients with Parkinson's disease compared to patients on drugs, or between those taking anticholinergic drugs and those not taking them. The

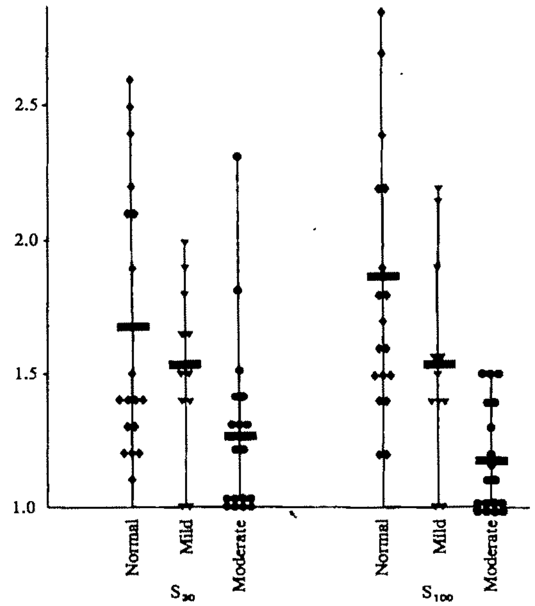

FIG. 7. Relative size of EMG responses in triceps suræ to stretch of the arm in normal subjects and in patients with mild and moderately severe Parkinson's disease. The size of the EMG response to stretch was measured 30 ms and 100 ms after its onset relative to the amount of EMG activity in randomly interspersed control runs (as described in Methods). Each point represents an individual subject. The solid bars indicate mean values. A ratio of 1.0 indicates that the records in stretch trials were identical to those in control runs.

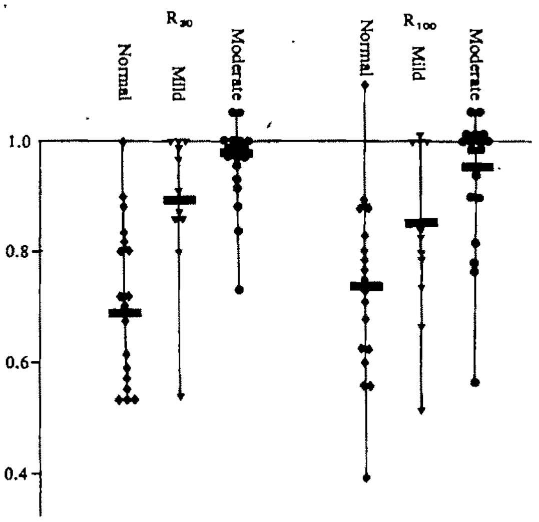

FIG. 8. Relative size of EMG responses in triceps suræ to release of the arm in normal subjects and in patients with mild and moderately severe Parkinson's disease. The size of the EMG response to release was measured 30 ms and 100 ms after its onset relative to the amount of EMG activity in randomly interspersed control runs (as described in Methods). Each point represents an individual subject. The solid bars indicate mean values. A ratio of 1.0 indicates that the records in release trials were identical to those in control runs.

differences between the patients and the normal control subjects were not due to differences in the extent to which the arm was stretched or pulled by the motor, for this was similar in all groups.

TABLE 1. RELATIVE SIZE AND LATENCY OF AUTOMATIC EMG RESPONSES IN TRICEPS SURÆ TO STRETCH AND RELEASE OF THE ARM IN NORMAL SUBJECTS AND PATIENTS WITH PARKINSON'S DISEASE

			Stretch		*Release*	
Group	*Age (yrs)*	*Latency (ms)*	S_{30} *ratio*	S_{100} *ratio*	R_{30} *ratio*	R_{100} *ratio*
Normals						
M 8	62±1.3	84±3	1.68	1.88	0.70	0.74
F 10			(1.4)	(1.6)	(0.7)	(0.75)
Parkinson's disease						
M 13	63±1.4	84±1.9	1.36	1.32**	0.94**	0.90**
F 16			(1.3)	(1.3)	(1.0)	(1.0)
Mild Parkinson's						
M 6	60±2.6	82±3	1.53	1.55	0.89*	0.84
F 5			(1.5)	(1.5)	(0.9)	(0.8)
Moderate Parkinson's						
M 7	65±1.6	86±2.6	1.26	1.17**	0.97**	0.94**
F 11			(1.2)	(1.1)	(1.0)	(1.0)

The size of the EMG responses to stretch (S) and release (R) at 30 and 100 ms after the perturbations are shown as a ratio of the EMG activity in randomly interspersed control runs (*see Methods*). Means (±1 SEM) for age and latency are shown; median values for the non-normal distributions of the ratio S_{30}, S_{100}, R_{30} and R_{100} are also given in brackets. Differences between patients and normal subjects significant at $P < 0.05$*, or $P < 0.01$**.

Progressive Supranuclear Palsy

The size of the response to stretch and release, together with their estimated latencies, is listed for the four subjects with progressive supranuclear palsy in Table 2. The average EMG response from subject A.K. is also illustrated in fig. 9B. In spite of their moderate to severe ataxia all four patients demonstrated essentially normal postural responses at the usual latency.

Cerebrovascular Disease

The results for the single patient (H.N.) are included in Table 2 and are illustrated in fig. 9C. The patient was grossly ataxic, but had an anticipatory postural response of normal latency and magnitude.

Table 2. Relative Size and Latency of Automatic EMG Responses in Triceps Suræ to Stretch and Release of the Arm in 4 Patients with Progressive Supranuclear Palsy (PSP) and in Patient H.N. with a Severe Akinetic Syndrome Secondary to Cerebral Ischæmia (CVD). The Mean Results of a Normal Control Group of the Same Age have been Inserted for Comparison

					Stretch		*Release*	
Patient	*Age (yrs)*	*Diagnosis*	*Severity of ataxia*	*Latency (ms)*	S_{30} *ratio*	S_{100} *ratio*	R_{30} *ratio*	R_{100} *ratio*
W.M.	52	PSP	++	92	1.92	1.53	0.88	0.86
G.W.	66	PSP	++	81	2.53	2.42	0.98	1.12
A.K.	68	PSP	+	87	2.13	1.82	0.53	0.58
O.Z.	70	PSP	+	87	1.25	1.44	0.58	0.59
H.N.	58	CVD	++	84	1.40	1.87	0.79	0.79
Normal (N = 18)	62±1.3			84±3	1.68	1.88	0.72	0.74
					(1.4)	(1.6)	(0.7)	(0.75)

Severity of ataxia: + = able to stand without support but more than 5 falls/day—no visible compensatory and protective responses to sudden lateral tilt; ++ = severely impaired—barely able to stand without support and no protective response to tilt. The size of the EMG responses to stretch (S) and release (R) at 30 and 100 ms after the perturbations are shown as a ratio of the EMG activity in randomly interspersed control runs (*see Methods*). In normal subjects means (±1 SEM) for age and latency are shown; median values for the non-normal distributions of the ratio S_{30}, S_{100}, R_{30} and R_{100} are also given in brackets.

Cerebellar Syndromes

The results from four patients with cerebellar truncal ataxia are shown in Table 3A. When the patients T.C. and K.G. had severe postural instability before the operation for their cerebellar tumours they lacked any automatic response, but after operation this returned to normal even though they were still moderately ataxic (fig. 10). Patients M.P. and M.D. with milder cerebellar syndromes who were able to walk unaided also had quite normal anticipatory postural responses.

Patients G.L. and S.C. with unilateral limb ataxia held the motor chain with their ataxic right arm. Both had a large anticipatory postural response at normal latency (Table 3B and fig. 9D).

Diphenylhydantoin Intoxication

When the three drug-intoxicated epileptic patients were examined initially they were moderately drowsy and exhibited severe postural instability. Patients J.A. and M.M. had no detectable response; patient R.C. produced a small burst of EMG activity. The response was restored in all three patients when they recovered (Table 4).

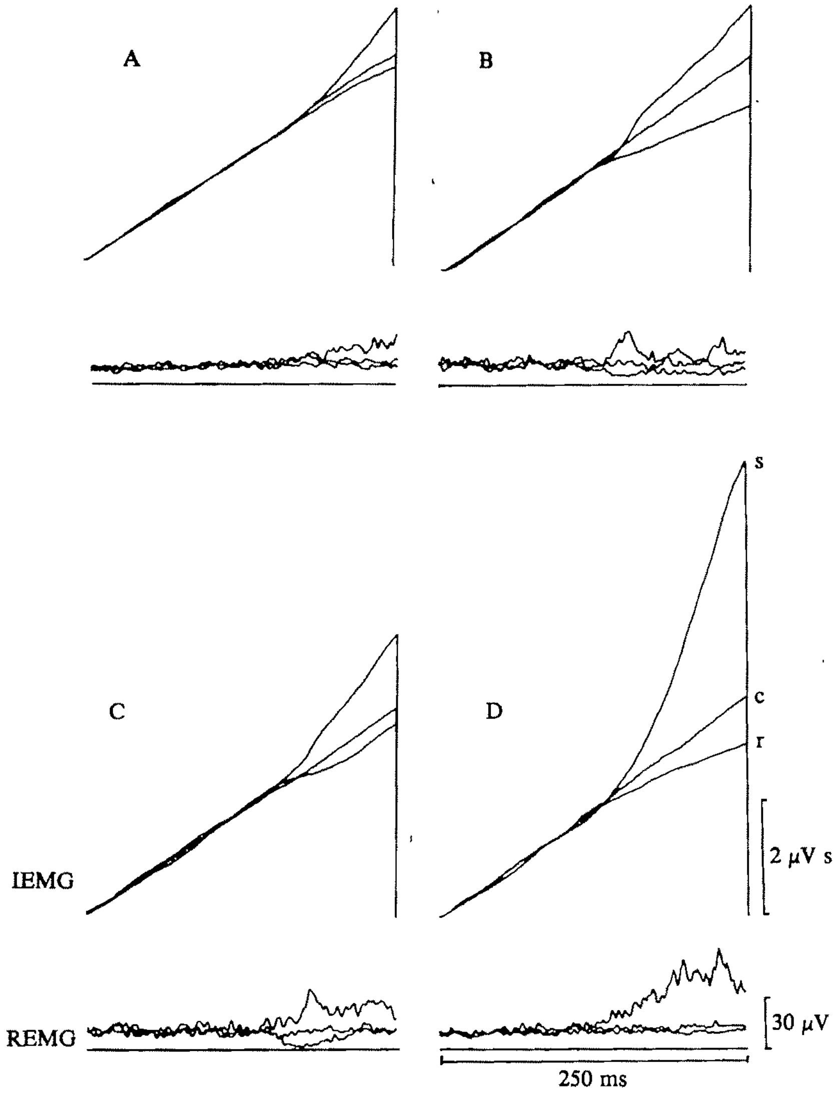

Fig. 9. Anticipatory postural responses in triceps suræ provoked by a pull to the arm. A, patient F.E. with hereditary spastic paraplegia exhibiting gross spasticity in his lower limbs, hyperactive tendon reflexes and extensor plantar responses, but no weakness. B, patient A.K. with progressive supranuclear palsy. C, patient H.N. with an akinetic rigid syndrome secondary to cerebrovascular disease. D, patient S.C. with a cerebellar astrocytoma, causing severe ataxia of his right arm (with which he held the motor chain). Average rectified (REMG) and integrated EMG (IEMG) traces are shown for 32 controls (c), stretches (s) and releases (r) in each patient.

TABLE 3A. RELATIVE SIZE AND LATENCY OF AUTOMATIC EMG RESPONSES IN TRICEPS SURÆ TO STRETCH AND RELEASE OF THE ARM IN 4 PATIENTS WITH CEREBELLAR TRUNCAL ATAXIA. PATIENTS K.G. AND T.C. WERE ALSO EXAMINED POST-OPERATIVELY

					Stretch		*Release*	
Patient	*Age (yrs)*	*Diagnosis*	*Severity of ataxia*	*Latency (ms)*	S_{30} *ratio*	S_{100} *ratio*	R_{30} *ratio*	R_{100} *ratio*
M.P.	24	Pontine glioma	+	69	2.32	1.34	0.69	0.59
M.D.	53	Idiopathic cerebellar degeneration	+	76	3.05	4.67	0.45	0.50
K.G.	62	Right acoustic neuroma	++	—	1.0	1.0	1.0	1.0
		Two weeks post-operatively	+	72	1.57	1.52	0.86	0.78
		Six months post-operatively	0	72	1.56	1.66	0.84	0.72
T.C.	29	Left cerebellar hæmangioblastoma hydrocephalus	++	—	1.0	1.0	1.0	1.0
		Three weeks post-operatively	+	78	1.31	1.52	0.77	0.75
		Three months post-operatively	0	75	1.39	1.60	0.77	0.71

Severity of ataxia: + = moderate. Broad-based gait. Able to rise from chair unaided. ++ = severe. Barely able to stand without support.

TABLE 3B. DATA FOR 2 SUBJECTS WITH LIMB ATAXIA WITHOUT POSTURAL INSTABILITY. THE PULL WAS TAKEN TO THE ATAXIC RIGHT ARM. RESULTS OF A GROUP OF YOUNG NORMAL SUBJECTS INSERTED FOR COMPARISON

					Stretch		*Release*	
Patient	*Age (yrs)*	*Diagnosis*	*Severity of limb ataxia*	*Latency (ms)*	S_{30} *ratio*	S_{100} *ratio*	R_{30} *ratio*	R_{100} *ratio*
S.C.	24	Right cerebellar astrocytoma	++	76	1.82	2.21	0.71	0.71
G.L.	46	Multiple cerebellar hæmangioblastomata	+	75	2.42	1.54	0.55	0.79
Normal (N = 18)	24±1.6	—	—	82±2.6	1.64 (1.6)	1.80 (1.7)	0.74 (0.7)	0.72 (0.75)

Severity of limb ataxia: + = moderate, ++ = severe. The size of the EMG responses to stretch (S) and release (R) at 30 ms and 100 ms after the perturbation computed as in Table 1. For normal subjects means (±1 SEM) for age and latency are shown; median values for non-normal distributions of the ratio S_{30}, S_{100}, R_{30} and R_{100} are also given in brackets.

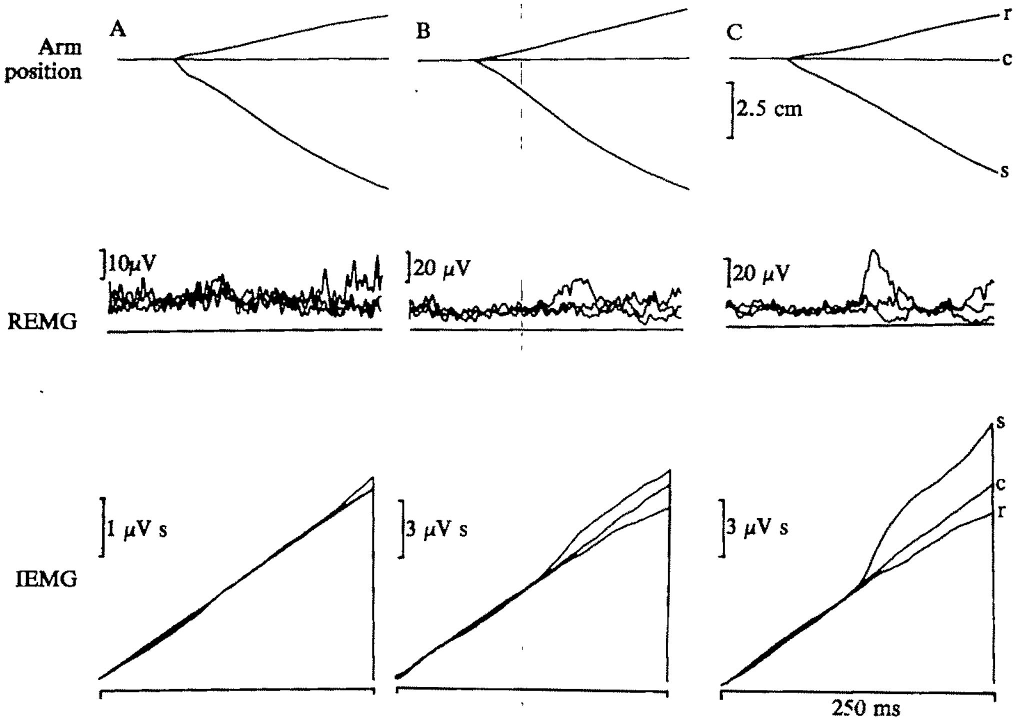

FIG. 10. Anticipatory postural responses in triceps suræ provoked by a pull to the arm in severely ataxic patient (T.C.) with a left cerebellar hæmangioblastoma. Traces are motor position (*top*), rectified EMG (REMG) (*middle*) and integrated rectified EMG (IEMG) (*bottom*). Averages of 32 control (c), stretch (s) and release (r) trials are shown in each group. A, before operation; B, three weeks after operation; C, three months after operation. *See text* for clinical details at these times.

TABLE 4. DATA FOR 3 EPILEPTIC PATIENTS DURING PHENYTOIN INTOXICATION AND AFTER RECOVERY

		Serum levels			*Stretch*		*Release*	
Patient	*Age (yrs)*	*μg/ml (normal range 10–20 μg/ml)*	*Severity of ataxia*	*Latency (ms)*	S_{30} *ratio*	S_{100} *ratio*	R_{30} *ratio*	R_{100} *ratio*
J.A.	63	34	++	—	1.00	1.00	1.00	1.00
		18	0	94	1.10	1.40	0.89	0.8
M.M.	58	36	++	—	1.00	1.00	1.00	1.00
		13	0	94	1.47	1.68	0.62	0.68
R.C.	54	29	++	—	1.10	1.21	0.92	0.91
		18	0	76	2.6	1.6	0.72	0.7

The size of the EMG responses to stretch (S) and release (R) at 30 ms and 100 ms after the perturbation as in Table 1.

Ethanol Intoxication

Fig. 11 shows the depression of the anticipatory postural response with increasing inebriation in a normal volunteer. The same result was also achieved in one of the authors.

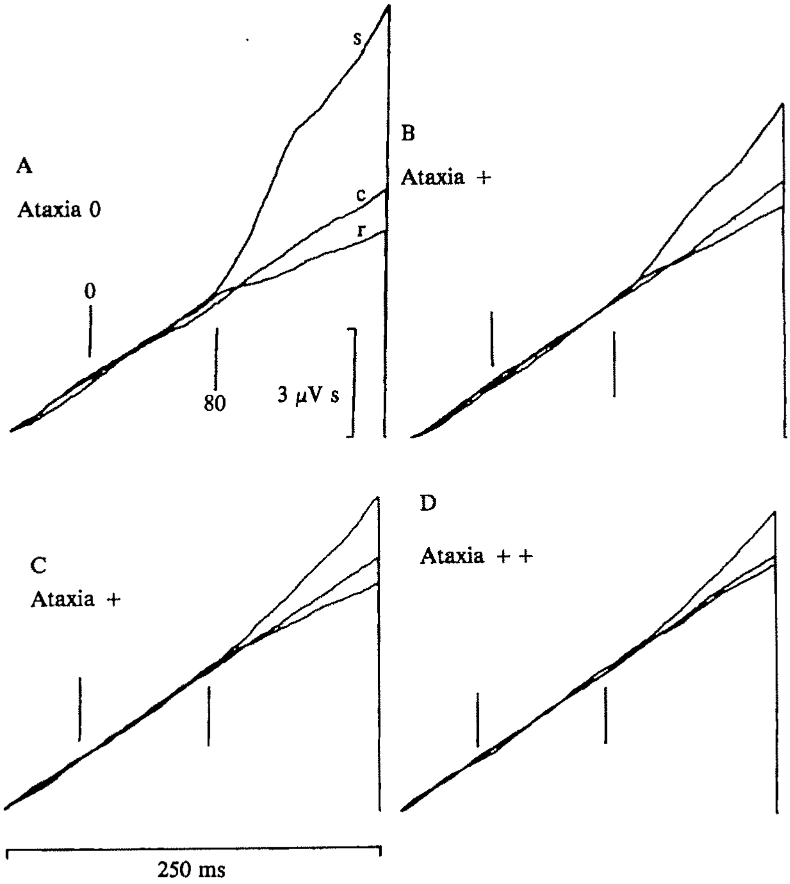

FIG. 11. Progressive diminution of the postural reflex during ethanol intoxication. A is the normal response of the subject, B, C and D are at 45 min intervals during ingestion of approximately 150 ml pure ethanol in orange juice. Postural ataxia: + = moderate, + + = severe. Average rectified and integrated EMG traces are shown from 32 control (c), release (r) and stretch (s) trials at each stage. The timing bars are at the time of the disturbance and 80 ms later.

Pyramidal Deficit

We examined four patients with moderate or severe spasticity, but with little or no weakness or sensory disturbance, in order to determine whether pyramidal deficit alone can alter the anticipatory postural response. Two patients had a normal response, whilst in the others it was delayed or depressed in contrast to the increase in their segmental tendon jerks (fig. 9A).

DISCUSSION

We have shown in normal standing subjects that a slight pull to the arm so as to tilt the trunk forward will cause a burst of EMG activity in the calf muscles, such as to oppose the body's sway. This response occurs too fast to be anything other than automatic and appears quite regularly in all normal subjects that we have studied. It cannot be produced by stretch of the calf muscles, for it precedes any detectable movement of the leg, and still occurs after the Achilles tendon jerk has been virtually abolished by regional intravenous injection of local anæsthetic. In this way it resembles the driven anticipatory postural reflexes described by Marsden *et al.* (1978), who showed that a pull to one arm could provoke distant responses in the opposite arm, trunk and legs, in muscles engaged in supporting the body, but in advance of any change in their length. They suggested that such driven distant anticipatory postural responses are stimulated by afferent input from the muscles stretched by the pull on the arm. They occur at latencies similar to those of the so-called, long-latency stretch reflexes that appear in an actively contracting agonist or prime mover, which may be due to a 'transcortical' mechanism (Marsden, Merton and Morton, 1976*a*, *b*) (Table 5). Perhaps anticipatory postural responses likewise are mediated by cerebral mechanisms. Stretch of a limb carrying out a task appears to set up a complex series of rapid automatic compensatory events including immediate contraction of the prime mover at monosynaptic and at longer latencies (the relative magnitudes of these two depending upon the muscle involved and the rate of stretch), and also rapid contraction in distant postural muscles actively engaged in stabilizing the limb and body.

TABLE 5. APPROXIMATE DELAY TO ONSET (MS) OF LONG LATENCY RESPONSES TO DIRECT MUSCLE STRETCH AND OF ANTICIPATORY POSTURAL RESPONSES IN THE SAME MUSCLES TO A PULL ON THE ARM

Muscle	*Triceps*	*Pectoralis major*	*Flexor hallucis longus*
Latency of direct stretch response	40	40	80–90
Latency of anticipatory postural response	55	40	80–90

From Marsden *et al.* (1976*b*, 1978), this paper and unpublished observations.

The anticipatory postural reflexes described in this paper and those of Marsden *et al.* (1978) must be compared to a number of similar events described by other authors. The so-called 'functional stretch reflex' described by Melvill Jones and Watt (1971) in calf muscle, and similar responses described by Gottlieb and Agarwal (1979) in the same muscles, were produced by dorsiflexing the ankle so as to directly stretch the calf muscles. The anticipatory postural response described here occurs with a shorter latency than the functional stretch reflex (approximately 120 ms) and Chan, Kearney and Melvill Jones (1979) have suggested that this response to direct stretch is not automatic, for it is delayed in patients with prolonged voluntary reaction times due to Parkinson's disease. Nevertheless, Nashner (1976, 1977) has described similar responses to calf muscle stretch produced by tilting a platform on which the subject stood, which he believes are totally automatic. He also observed responses in different muscles such as hamstrings and sacrospinalis which may not have been due to direct muscle stretch, but from the data available it is not possible to decide on this point. None of these events closely resembles the driven anticipatory postural responses described here.

Study of anticipatory postural reflexes in calf muscles in response to a pull on the arm in standing patients with Parkinson's disease has revealed interesting abnormalities. The reflexes were grossly reduced or absent in those patients who exhibited postural instability and sometimes were diminished even in those patients who appear stable. We were able easily to find such anticipatory postural reflexes in every one of the 50 normal subjects we have examined. They were absent or scarcely detectable in 10 of the 18 patients with moderately severe Parkinson's disease and postural instability, and in 2 of the 11 patients with mild Parkinson's disease and no obvious instability. It may be more important, however, to note that clear-cut anticipatory postural reflexes in calf muscles were present in 8 of the 18 patients with moderate Parkinson's disease and obvious clinical postural instability, and the magnitude of these responses was within the range of normal in most of these patients. Accordingly, patients with Parkinson's disease can still fall despite apparently normal anticipatory reflexes as tested here. Other ataxic patients also had normal anticipatory postural responses to a pull on the arm. The 4 patients with progressive supranuclear palsy and the single patient with cerebrovascular disease had normal responses despite exhibiting marked unsteadiness of gait and falling frequently. Likewise, those patients with mild to moderate cerebellar ataxia also had normal responses. The overall conclusion must be that severe basal ganglia and cerebellar disease can interfere with anticipatory postural responses but if mild, such lesions do not apparently alter the responses despite obvious unsteadiness. The cerebral pathways involved in these responses is not known but may not involve the basal ganglia and cerebellum. As far as the latter is concerned it is of interest to note that brisk postural responses were obtained in the ipsilateral leg when the pull was given to the affected arm in 2 patients with unilateral cerebellar ataxia. It is also of interest that lesions apparently restricted clinically to the corticomotor neuron ('pyramidal') pathway may abolish anticipatory postural responses, but not in every case.

The stimulus to these anticipatory postural reflexes was only a small pull on the arm insufficient to cause visible protective reactions even in normal subjects. A quite firm push or large tilt is required to demonstrate the defective protective and equilibrating reactions demonstrated by Martin (1967) in patients with Parkinson's disease. Such large disturbances might unearth abnormalities in unstable patients which were not detected by the much smaller movements used in the present study. The physiological mechanisms employed to compensate for such large disturbances may differ from those used to adjust to small perturbations. While anticipatory postural responses may operate for body sway induced by pulling on one arm, separate mechanisms may be required to maintain balance during normal walking, or in response to large shifts in body position.

SUMMARY

We have examined anticipatory postural responses in calf muscles (triceps suræ) in response to a small pull to the arm in standing subjects. This stimulus normally evokes a brisk automatic compensatory contraction of the calf muscles. This is not due to calf muscle stretch, for leg movement occurs after the response has appeared. It appears to be driven centrally by input produced by the pull to the arm. Such anticipatory postural responses were present in every one of the 50 normal subjects studied, but were absent or greatly reduced in many patients with Parkinson's disease when compared to age-matched normal subjects, particularly in those exhibiting postural instability. However, a normal anticipatory postural response was elicited in four patients with progressive supranuclear palsy and in a single patient with an akinetic rigid syndrome due to cerebrovascular disease. Cerebellar truncal ataxia only depressed the response in severe cases. We conclude that although these responses may not be necessary to maintain balance, they may be employed in fine adjustment of posture.

ACKNOWLEDGEMENTS

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THE INCIDENCE AND NATURE OF VISUAL PATHWAY INVOLVEMENT IN FRIEDREICH'S ATAXIA

A CLINICAL AND VISUAL EVOKED POTENTIAL STUDY OF 22 PATIENTS

by W. M. CARROLL, A. KRISS, M. BARAITSER, G. BARRETT *and* A. M. HALLIDAY

(From the Medical Research Council, Institute of Neurology, National Hospital for Nervous Diseases, Queen Square, London WC1N 3BG, the Division of Inherited Metabolic Disease, Northwick Park Hospital, Harrow, Middlesex)

INTRODUCTION

SINCE Friedreich (1863) first differentiated the condition from tabes dorsalis there have been many clinical, pathological and genetic reports identifying the disease as a separate entity from other familial, sporadic and acquired ataxias. The widespread involvement of both the peripheral and central nervous systems, which results in the characteristic progressive clinical picture and post-mortem pathological appearance, in association with a cardiomyopathy and frequently with a disturbed carbohydrate metabolism, have suggested an underlying metabolic disorder. However, despite evidence in some patients with Friedreich's ataxia of a defective pyruvate dehydrogenase enzyme system (Kark, Blass and Engel, 1974; Kark and Rodriguez-Budelli, 1979), an abnormal high density lipoprotein composition of the serum (Huang, Nestruck, Barbeau, Bouchard and Davignon, 1978), selective aminoaciduria (Lemieux, Barbeau, Beroniade, Shapcott, Breton, Geoffroy and Melançon, 1976) and hyperbilirubinæmia (Barbeau, Breton, Lemieux and Butterworth, 1976) a specific and characteristic metabolic disturbance has not been found (Melançon, Potier, Dallaire, Fontaine, Grenier, Lemieux, Geoffroy and Barbeau, 1978; Baraitser, Borud, Chalmers and Purkiss, 1980; Barbeau, 1979; Stumpf and Parks, 1979).

Although the ætiology of Friedreich's ataxia remains obscure, more is known of the nature of the disease process, especially in the peripheral nervous system. Dyck and Lais (1973) have extended the earlier observations of Hughes, Brownell and Hewer (1968) and concluded that there is a progressive, initially large fibre, axonal degeneration with accompanying clustered segmental demyelination. Peripheral nerve electrophysiological studies are consistent with this concept (Dyck, Lambert and Nichols, 1971; McLeod, 1971; Oh and Halsey, 1973; Salisachs, Codina and Pradas, 1975; Peyronnard, Lapointe, Bouchard, Lamontagne, Lemieux and Barbeau, 1976). By comparison, however, little is known of the pathophysiology of the process in central pathways. Technical constraints have prevented the application of a detailed morphometric analysis, similar to that used in the peripheral nerves, to define the early lesion in the less severely affected central pathways.

As part of a larger study of this disorder we have employed the technique of visual evoked potential (VEP) recording to examine a central nervous system pathway in 22 patients with typical Friedreich's ataxia. We were particularly interested in the following aspects. First, because the incidence (Bell and Carmichael, 1939; Sjögren, 1943; Wilson, 1954; Heck, 1964; Geoffroy, Barbeau, Breton, Lemieux, Aube, Leger and Bouchard, 1976; Andermann, Remillard, Goyer, Blitzer, Andermann and Barbeau, 1976) and the nature (Urich, Norman and Lloyd, 1957; Boudin, Grossiord, Guillard, Mikol and Lacert, 1972; Oppenheimer, 1976) of visual involvement is not well documented in the literature, we used a number of neuro-ophthalmic and VEP parameters to define these aspects. Secondly, we wished to determine whether the conclusions based on studies of the peripheral nervous system as to the pathophysiology of the disease were consistent on electrophysiological grounds with the findings in a relatively asymptomatic central pathway such as the visual system. Finally, we were interested to see if the VEP findings in Friedreich's ataxia differed significantly from those found in predominantly demyelinating optic neuropathies.

PATIENTS AND METHODS

Thirteen male and 9 female patients from volunteers of the Friedreich's Ataxia Association who lived within a 20-mile radius of the centre of London were selected on the clinical and genetic criteria established by the Quebec Co-operative Study of Friedreich's Ataxia (Barbeau, 1976). The mean age of the group was 33.7 years, the mean age of onset of generalized symptoms was 11.5 years and the mean duration of the disease when studied was 22.1 years. All but one were affected before the age of 20 years. The mode of inheritance was compatible with autosomal recessive transmission and none of the 20 families had two generations affected. Consanguinity featured in three of the families. All 22 patients had typical cerebellar ataxia, dysarthria, moderate to severe posterior column sensory disturbance, areflexia and progression without remission of symptoms from the time of onset. All but one had varying degrees of weakness and mild to moderate distal muscle wasting. Bilateral extensor plantar responses, scoliosis and pes cavus were each present in 70 per cent of the patients. Non-specific electrocardiographic changes suggesting the presence of cardiomyopathy and a variable disturbance of ocular movements were found in 60 per cent. Seven (31 per cent) had biochemical evidence of impaired carbohydrate metabolism. None of the 22 had noted sudden or gradual impairment of vision and none were demented.

Fifteen of the 22 patients underwent a detailed neuro-ophthalmological assessment prior to the VEP examination which included recording the corrected visual acuity (Snellen charts), colour vision

(Ishihara test plates), mapping of the visual fields and ophthalmoscopy. The degree of temporal or generalized pallor of the discs was assessed, the number of small vessels crossing the disc margin that could not be identified as arteries or veins (Veith and Sacks, 1973) was recorded and the retina was examined for evidence of degenerative or diabetic changes. The remaining 7 subjects had only their corrected visual acuity recorded. Observations on the number of small vessels crossing the optic disc margin and errors of colour vision had previously been made on 75 normal subjects aged between 5 and 61 years (Carroll and Mastaglia, 1979). Three (4 per cent) of these made a single error with the Ishihara plates and none took longer than five seconds to correctly identify each plate. All 150 eyes had 7 or more small vessels crossing the disc margin except for 2 which had 6 (mean 8.7, range 6–13).

Monocular VEPs were obtained by an established technique (Halliday, Halliday, Kriss, McDonald and Mushin, 1976) from an 8 channel electrode montage, comprising transverse and sagittal chains. The midline electrode of the transverse chain of 5 was 5 cm above the inion and all 8 electrodes were referred to a midfrontal electrode. Visual stimulation was provided by a back-projected black-and-white checkerboard pattern reversed every 605 ms by lateral displacement using a rotating mirror. The transition time for the reversal of the pattern was 10 ms. Each check had a visual subtense of 50 min and the luminance of the black-and-white checks was 8.2 cd m^{-2} and 227 cd m^{-2}, respectively. The occipital responses were averaged by a purpose-built averager triggered by each pattern reversal, and the averaged response to 200 such reversals was recorded on digital magnetic tape. Responses were obtained from each eye to wide-field (16 deg radius), central-field (4 deg radius) and right and left vertical half-field (16 deg radius) stimulation with all subjects wearing spectacles when appropriate. The amplitude and latency of the response components were cursored peak-to-peak from the preceding wave of opposite polarity as determined by visual inspection. The principal response component analysed was the $\overline{\mathrm{P100}}$ recorded from the midline electrode after wide and central-field stimulation and the same component recorded from the ipsilateral electrode 5 cm lateral to the midline after half-field stimulation (Blumhardt, Barrett, Halliday and Kriss, 1978). The temporal dispersion of the $\overline{\mathrm{P100}}$ component was also assessed by determining the latency difference between the preceding ($\overline{\mathrm{N80}}$) and following ($\overline{\mathrm{N145}}$) negative components. The interocular differences in $\overline{\mathrm{P100}}$ latency and amplitude and the $\overline{\mathrm{P100}}$ central-field/wide-field amplitude ratio were also determined. All these parameters were compared to normal values obtained from 31 healthy subjects by taking the mean ±2.5 standard deviations as the upper and lower limits of normal.

Electroretinograms (ERG) from one eye were recorded from 3 selected patients with corneal electrodes using an established technique and a number of scotopic and photopic parameters were studied (Ikeda, 1976). These included the rise in ERG amplitude during dark adaptation, the dark-adapted threshold, the ERG wavelet amplitude as a function of red light flicker frequency and the ERG to different wavelengths of light.

RESULTS

Clinical Neuro-ophthalmic Findings

These are summarized in Table 1. The visual acuity was 6/12 or worse bilaterally in 6 subjects and 4 more (excluding Case 22 who had sustained a penetrating left eye injury in the past) had a similar unilateral acuity level. Apart from Case 22, no patient had a visual acuity worse than 6/24. Of the 13 in whom colour vision was tested, 4 showed mild bilateral and one unilateral impairment. Nine of the 15 patients who underwent the neuro-ophthalmic examination had bilateral and 2 more had unilateral mild to moderate temporal pallor but none had marked optic atrophy. Case 22 had moderate generalized disc pallor in the previously injured eye. Reduced numbers of small vessels crossing the disc margin were found bilaterally in 4 of the 9 patients with binocular temporal pallor and 3 more (one with only unilateral temporal pallor) showed a monocular reduction in the small vessel count. None, however, had less than 5 vessels on the disc margin. Six of the 13 subjects in whom the number of vessels were quantified had a normal count. None of the 14 clinically abnormal patients (*see below*) were so classified solely on this parameter. The peripheral retina was normal in all the 15 subjects, and none had visual field defects.

On the basis of the neuro-ophthalmic examination the 22 patients could be divided into three groups (Table 1): (1) clinically abnormal (Cases 1–14); (2) clinical status unknown but with normal visual acuity (Cases 15–18); (3) clinically normal (Cases 19–22). The criteria used to define the presence of clinical neuro-ophthalmic abnormality was one or more of the following abnormalities in one or both eyes: (a) a best corrected visual acuity of 6/12 or worse; (b) two or more errors of colour vision; (c) temporal or generalized pallor of the optic disc; (d) less than 7 small vessels crossing the disc margin; (e) a central or peripheral field defect.

Of the 15 who underwent the detailed clinical neuro-ophthalmic examination 10 (67 per cent) had two or more abnormal clinical parameters and one additional patient, Case 9, had one abnormal parameter, making a total of 73 per cent. Three patients were classified as clinically abnormal without the complete assessment because of visual acuities of 6/12.

VEP Findings

Prolongation of the $\overline{\mathrm{P100}}$ latency or the absence of a response defined an abnormal VEP study in 14 (8 male and 6 female) of the 22 patients (64 per cent). Of these 14 patients the 13 who had the complete VEP examination had 4 or more abnormal studies out of the 2 wide-field, 4 half-field and 2 central-field recordings made from each (Table 1). The most frequent abnormality was prolongation of the $\overline{\mathrm{P100}}$ component latency (Table 2) and 11 of the 14 patients showed only this abnormality for the wide-field stimulus (Table 1), of which fig. 1 is a typical example. The maximum wide-field $\overline{\mathrm{P100}}$ latency recorded was 143 ms. Three patients (Cases 1, 2 and 8) who had an abnormal VEP examination had both delayed responses and other responses which were either absent or abnormal in waveform (Table 1, fig. 2). Only one individual (Case 22, with an old left intraocular injury) had an absent half-field and central-field response with normal latencies for the other responses (Table 1). The mean latency of the 12 patients with delayed wide-field responses was 127 ms and the value was similar for the other modes of stimulation (Table 3).

The interval between the negative peaks preceding and following the $\overline{\mathrm{P100}}$ component, taken as an index of temporal dispersion of response, did not add to the number of abnormal VEP studies and this parameter and the response

TABLE 1. CLINICAL NEURO-OPHTHALMIC AND VEP FINDINGS FOR EACH OF THE 22 PATIENTS WITH TYPICAL FRIEDREICH'S ATAXIA

Case	Sex	Age (yrs)	Duration (yrs)	Visual acuity		Colour vision errors*		Visual fields		Disc appearance		Reduced small vessel count ($\leqslant 6$)		VEP findings					
														Wide-field		Half-fields		Central field	
				L	R	L	R	L	R	L	R	L	R	L	R	L(2)	R(2)	L	R
Abnormal clinical neuro-ophthalmic examination																			
1	F	25	10	6/18	6/18	3	3	N	N	T2	T3	—	—	D	A	—	—	—	—
2	M	31	20	6/18	6/18	1	2	N	N	T2	T2	6	5	D	D	1A1D	1A1D	A	A
3	F	54	40	6/18	6/24	—	—	—	—	—	—	—	—	D	D	2D	2D	D	D
4	M	36	30	N	N	2	1	N	N	T2	T2	N	N	D	D	2D	2D	D	D
5	M	37	23	N	N	N	N	N	N	T2	T2	6	5	D	D	2D	2D	D	D
6	M	36	19	N	N	N	N	N	N	T1	T1	N	6	D	D	1D	1D	N	N
7	F	20	15	N	6/12	N	2	N	N	T1	T1	N	N	D	D	2D	2D	D	D
8	M	23	15	6/18	6/18	—	—	—	—	—	—	—	—	Ø	Ø	1D	1D		A
9	M	57	22	N	N	N	N	N	N	T1	N	N	N	D	D	1D	1D	D	D
10	F	33	23	6/12	6/12	N	N	N	N	N	T1	N	6	D	D	2D	2D	D	D
11	F	50	36	N	6/12	N	N	N	N	T1	T2	6	6	D	D	2D	1D	D	D
12	F	26	19	N	6/12	4	4	N	N	T2	T2	6	N	D	D	1D	2D	N	N
13	F	32	21	6/12	6/18	N	N	N	N	T1	T1	5	5	N$^{\otimes}$	N$^{\otimes}$	N	N	N	N
14	M	31	16	N	6/12	—	—	—	—	—	—	—	—	N	N	N	N	N	N
Clinical neuro-ophthalmic status unknown																			
15	M	9	2	N	N	—	—	—	—	—	—	—	—	D	D	1D	2D	D	N
16	M	39	26	N	N	—	—	—	—	—	—	—	—	N	N	—	—	N	N
17	M	44	30	N	N	—	—	—	—	—	—	—	—	N	N	2D	1D	D	D
18	M	34	20	N	N	—	—	—	—	—	—	—	—	N$^{\otimes}$	N	N	N	N	N
Normal clinical neuro-ophthalmic examination																			
19	M	54	41	N	N	N	N	N	N	N	N	—	—	N	N	N	N	N	N
20	F	13	1	N	N	—	—	N	N	N	N	N	N	N	N	N	N	—	—
21	F	29	19	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
22	M	28	19	6/36	N	—	—	N	N	P2	N	N	N	N	N	1A‡	N	A‡	N

Key to Table 1

N = normal values. — = not examined. * number of Ishihara test plate errors (7 plates per eye). T = temporal pallor of optic disc (graded 1–4). P = generalized pallor of optic disc (graded 1–4). D = delayed (increased latency) VEP. A = absent VEP. Ø abnormal waveform (*see text*). ⊗ Abnormal central field/wide-field $\overline{\text{P100}}$ amplitude ratio (*see text*). ‡ Old intra-ocular trauma (*see text*). The figures (1 and 2) in the half-field column indicate the number of responses absent or delayed. (*See text* for further details).

TABLE 2. SUMMARY OF THE VEP FINDINGS FOR EACH MODE OF STIMULATION.

	Prolonged P100 latency	*Absent response*	*Abnormal response morphology*	*Normal*	*Total*
Wide-field:* (0–16 deg radius)	23/52% (11)	1/2%	2/4% (1)	18/42% (9)	44 eyes
Central field: (0–4 deg radius)	17/42.5% (8)	*4/10% (1)	1/2.5%	18/45% (8)	40 eyes
Half-fields: Left (0–16 deg radius)	20/50% (7)	*2/5%	—	18/45% (6)	40 eyes
Right	20/50% (7)	1/2.5%	—	19/47.5% (7)	40 eyes

Includes Case 22 with previous monocular trauma. The figures in parenthesis indicate the number of patients in whom the findings were bilateral.

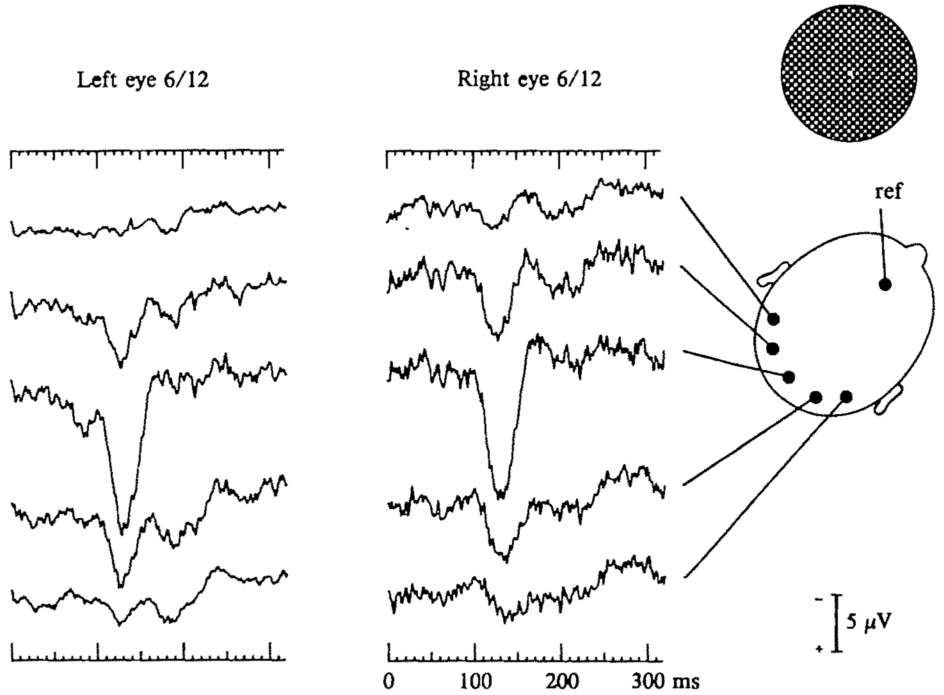

FIG. 1. Monocular wide-field (16 deg radius) VEPs from Case 10, a 33-year-old female whose symptoms of Friedreich's ataxia commenced at the age of 10 years, showing increased P100 component latencies of 131 ms and 129 ms for the left and right eyes (upper limit of normal, 115 ms). Of note is the normal waveform, amplitude and temporal dispersion of the response, and the similarity of the response from each eye. The clinical neuro-ophthalmic findings are detailed in Table 1. (Note: only the transverse chain of five electrodes are shown in this and subsequent VEP figures.)

TABLE 3. MEANS AND STANDARD DEVIATIONS OF THE P100 LATENCY FROM 21 FRIEDREICH'S ATAXIA PATIENTS, THOSE WITH ABNORMAL P100 LATENCIES AND HEALTHY NORMAL SUBJECTS FOR EACH MODE OF STIMULATION

	Wide-field (0–16 deg radius) ms	*L. half-field (0–16 deg radius) ms*	*R. half-field (0–16 deg radius) ms*	*Central field (0–4 deg radius) ms*
All Friedreich's ataxia subjects	118 (±11.6) (n = 21)	118 (±12.7) (n = 20)	119 (±13.6) (n = 20)	117 (±11.8) (n = 18)
Friedreich's ataxia subjects with prolonged latencies (> 115 ms)	127 (± 7.5) (n = 12)	129 (± 7.0) (n = 13)	130 (± 7.5) (n = 13)	127 (± 8.0) (n = 10)
Healthy control subjects	105 (± 4.0) (n = 31)	105 (± 4.0) (n = 20)	106 (± 4.2) (n = 20)	106 (± 4.7) (n = 31)

n = number of subjects in each group

waveform were normal in most patients, including those with an increased P100 latency. Interocular latency and amplitude differences (Table 4) were also normal for wide and central-field stimulation in all subjects with identifiable P100 components apart from those recorded from the affected eye of Case 22 in whom a reduced response amplitude was expected.

The VEP findings for each mode of stimulation are shown separately for individual patients in Table 1 and summarized in Table 2. Apart from Cases 1, 8, 15 and 17 the findings demonstrate a high degree of symmetry of abnormality with only Case 22 having purely monocular VEP abnormalities. Cases 1 and 8 had very low amplitude responses, just recognizable above the background activity, which would account for the abnormal waveform and interocular asymmetries (*see below*). The differences in the responses from the two eyes of Cases 15 and 17 (Table 1) are more apparent than real, as all their responses were at or above the

TABLE 4. MEANS AND STANDARD DEVIATIONS OF THE INTEROCULAR P100 LATENCY AND AMPLITUDE DIFFERENCES FOR FRIEDREICH'S ATAXIA AND NORMAL SUBJECTS AFTER WIDE AND CENTRAL FIELD STIMULATION

	Wide-field (0–16 deg radius)		*Central field (0–4 deg radius)*	
	FA	*Normals*	*FA*	*Normals*
Latency (ms)	1.12 (±3) (20)	0.6 (±2.5) (31)	2.1 (±6) (17)	1.1 (±2.6) (31)
Amplitude (μV)	0.25 (±2.1) (20)	0.6 (±1.9) (31)	0.3 (±1.2) (17)	0 (±1.32) (31)

There was no significant difference between the results for the two groups. The figures in parenthesis represent the number of subjects.

upper latency limit but only those responses exceeding the limits are shown as abnormal. The responses recorded from all 20 patients who had half-field stimulation in general agreed with the wide-field and central-field findings (Table 2). The half-field responses also assisted component identification. Apart from Case 1 where half-field stimulation was not performed, delayed wide-field responses were all confirmed as $\overline{\text{P100}}$ components (Blumhardt *et al.*, 1978). The abnormal waveform from both eyes in Case 8 (Table 1) comprised poorly defined and low amplitude positive-negative-positive complexes with the latency of the negativities being 100 ms. The half-field responses showed that the wide-field complexes resulted from the summation of a normal latency response from one half-field and a delayed response from the other half-field of each eye.

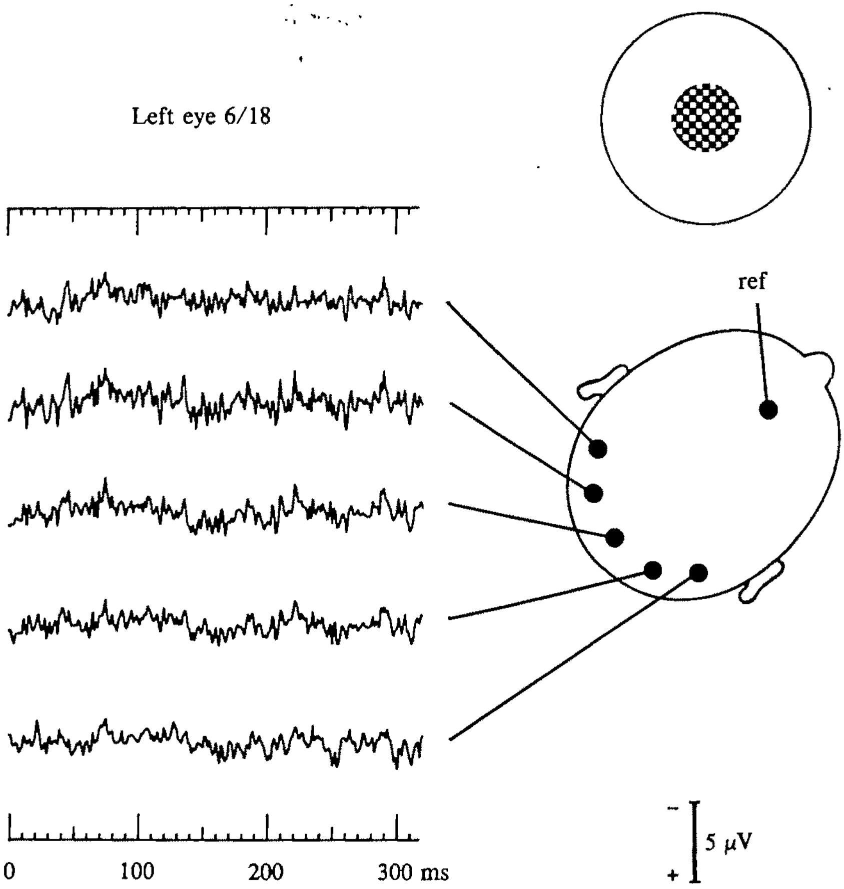

FIG. 2. Monocular central field (4 deg radius) VEP from Case 2, a 31-year-old male whose clinical neuro-ophthalmic findings are summarized in Table 1, showing the absence of an identifiable response.

Electroretinogram Findings

Electroretinograms were obtained from 3 patients whose VEP findings were either representative of the VEP abnormalities of the group (Cases 1 and 10) or showed an unusual abnormality (Case 8). The ERGs recorded from the left eyes of Cases 1 and 10 were just subnormal and remarkably similar, yet although both patients had delayed VEPs (fig. 1) the $\overline{\text{P100}}$ amplitude from Case 1 was very low. The ERG recordings of these two patients indicated minimally impaired cone-mediated function (reduced amplitude of flicker ERG wavelets) but normal ERG amplitude changes with dark adaptation and normal scotopic b-wave thresholds. The ERG from the right eye of Case 8 showed slightly more impairment of retinal function. In addition to the attenuated flicker ERG wavelets, the scotopic b-wave threshold was slightly raised. Thus, the reduction in retinal function determined by the ERGs in all 3 patients was relatively mild and even in Case 8 it was unlikely to account for the low amplitude VEP responses (Ikeda, H., personal communication).

Clinical and VEP Correlation

There was good correlation between the clinical neuro-ophthalmic findings and the VEP results (Table 1, fig. 3). All 4 patients classified as clinically normal had normal VEP studies, and 12/14 (86 per cent) of those in the clinically abnormal

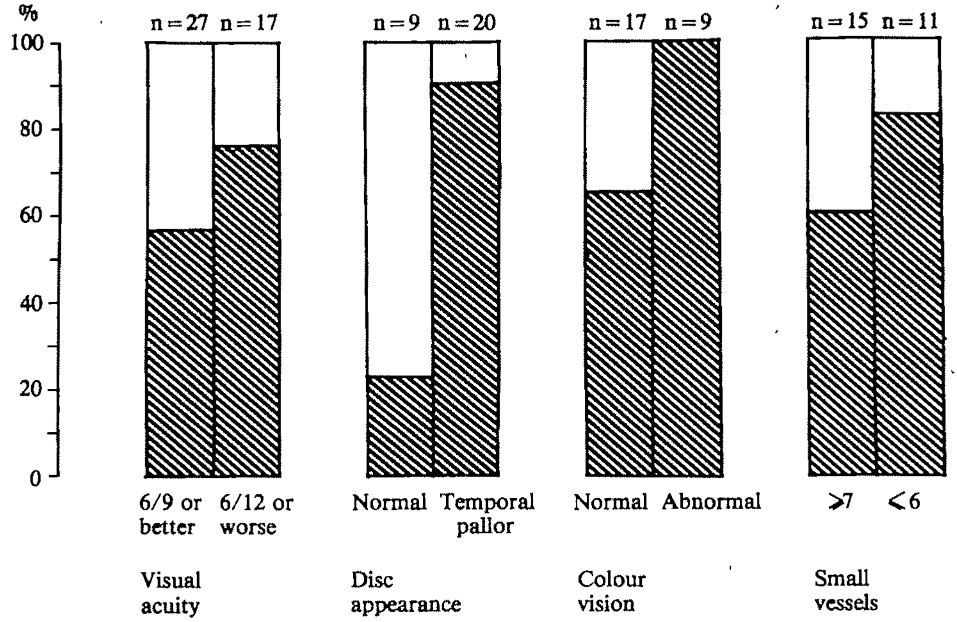

FIG. 3. Histograms for each clinical neuro-ophthalmic parameter (normal and abnormal) and the accompanying VEP result. The appearance of the optic disc correlated best with the VEP status ($P < 0.0003$). Although other clinical neuro-ophthalmic parameters were frequently normal when the VEP was abnormal, the converse was uncommon. ▨ abnormal VEP; ☐ normal VEP; n = number of eyes.

group had VEP abnormalities. The remaining 2 clinically abnormal subjects (Cases 13 and 14), had normal VEP parameters. However, the response amplitudes from Case 14 were all low (fig. 4), and the central-field/wide-field $\overline{\text{P100}}$ amplitude ratios were abnormal at 1.32 (upper limit 1.09) and 1.33 (upper limit 1.10) for the left and right eyes of Case 13. The significance of the abnormal amplitude ratios found in both eyes of Case 13 and from one eye in Case 18, with an otherwise normal VEP study is uncertain. As a group the Friedreich's ataxia subjects had a much wider variation in this amplitude parameter than normals (variance ratio; $F_{34,61} = 2.24$, $0.001 < P < 0.01$).

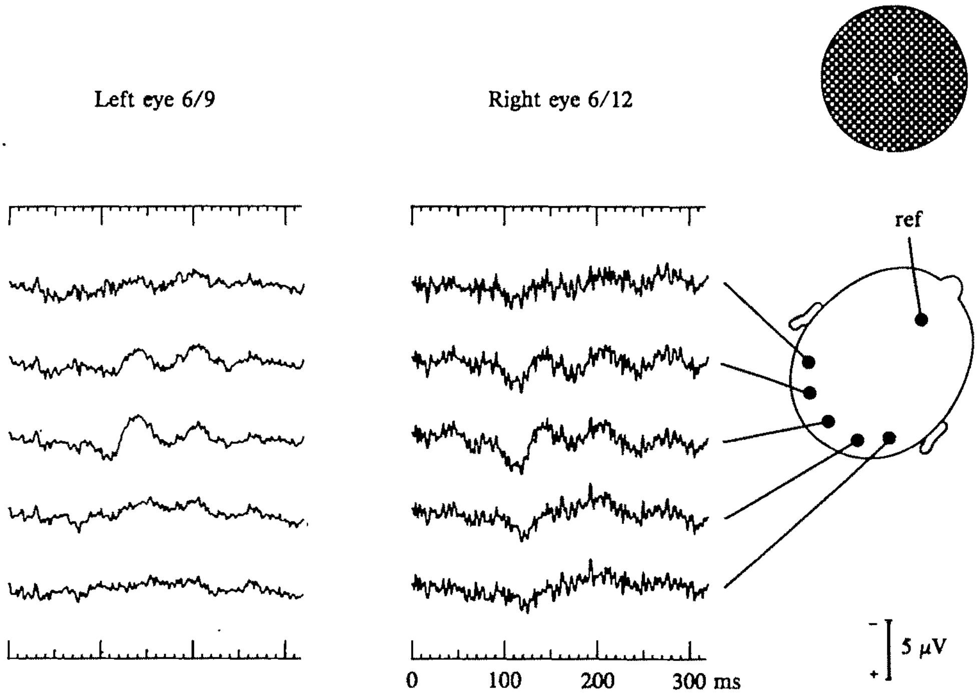

FIG. 4. Monocular wide-field (16 deg radius) VEPs from Case 14, a 31-year-old male who did not have a detailed neuro-ophthalmic examination (Table 1) showing very low amplitude normal latency $\overline{\text{P100}}$ components (left eye 112 ms, right eye 110 ms)

Although the individual clinical neuro-ophthalmic indices showed a good correlation with VEP status (Table 1, fig. 3), the only clinical parameter which was consistently associated with an abnormal VEP result was the appearance of the optic disc. Temporal pallor of the disc was found in 11 patients, 10 of whom had an abnormal VEP study (Fisher exact probability test $P < 0.0003$). Conversely, disc pallor was found in only one (Case 13) of the 5 patients with normal VEPs in whom ophthalmoscopy was performed. The other clinical parameters were less frequently abnormal but when dyschromatopsia or reduced small vessel numbers on the disc margin or impaired visual acuity were found, the chance of an abnormal VEP result was high. The absent responses found in Cases 1, 2 and 8 were associated with more marked neuro-ophthalmic abnormalities and in all 3 the visual acuity was 6/18. There was a significant correlation between the visual acuity and the wide-field $\overline{\mathrm{P100}}$ amplitude (fig. 5) but no relationship was found between the $\overline{\mathrm{P100}}$ latency and the acuity.

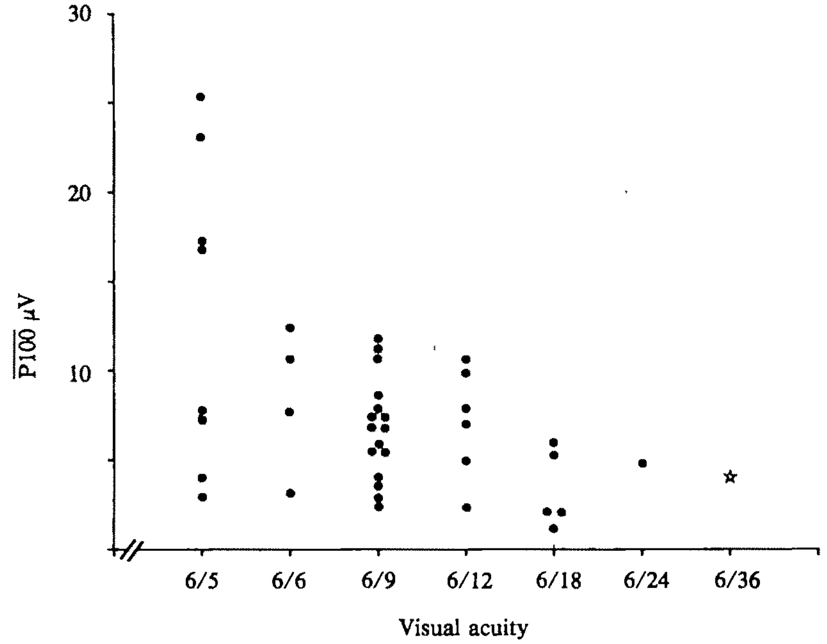

FIG. 5. Relation between the wide-field (16 deg radius) $\overline{\mathrm{P100}}$ amplitude and the visual acuity (Spearman rank order correlation coefficient, $r_{42} = 0.5$, $P < 0.001$). The open star indicates the VEP recorded from the left eye of Case 22 (*see text* for details).

Wide-field $\overline{\mathrm{P100}}$ amplitude decreased with the duration of the illness (fig. 6) although the few patients with durations of between three and fifteen years is to be noted. There was no correlation between duration of illness and $\overline{\mathrm{P100}}$ latency.

Group and Comparative VEP Analysis

Although only 3 patients had one or more absent response the amplitude in those with identifiable wide-field VEPs was generally reduced with a group mean of 7.6 μV (±5.3) as compared to normals (14.03±5.5). The VEP changes are more

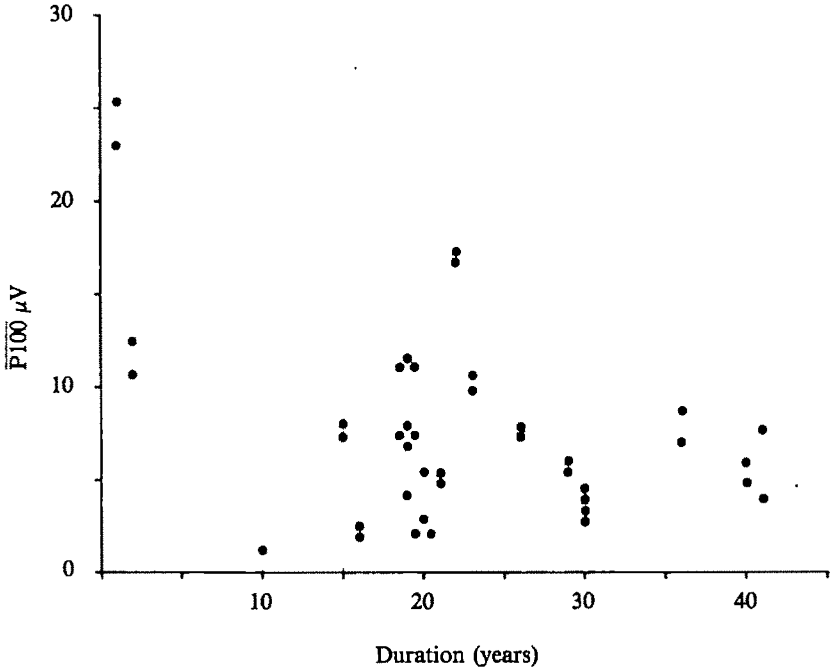

FIG. 6. Relation between the wide-field $\overline{\text{P100}}$ amplitude and the duration of the generalized disease symptoms; *viz.* ataxia and dysarthria. (Product moment correlation coefficient, $r = 0.48$, $P < 0.02$; two-tail test).

readily apparent when the amplitude and latency of each wide-field $\overline{\text{P100}}$ component is plotted and compared to those of the 31 normal subjects (fig. 7). Many of the Friedreich's ataxia $\overline{\text{P100}}$ amplitudes were less than 6 µV, the lowest amplitude recorded in the healthy control group.

In fig. 7 there is an apparent separation of the Friedreich's ataxia patients into two groups. This grouping did not follow the clinical divisions, although those with clinical abnormalities tended to cluster in the larger of the two VEP groups. The latter group comprised those patients with $\overline{\text{P100}}$ latencies of 116 ms or higher (upper limit of normal 115 ms). In this group there was a highly significant inverse correlation between the latency and amplitude ($r_{21} = 0.72$; $P < 0.001$) and all the individuals were from the abnormal or unknown clinical neuro-ophthalmic divisions. The second VEP group which was clinically more heterogeneous all had normal VEP latencies but most, however, had VEP amplitudes of less than 6 µV. When compared with the 26 VEPs from the affected eyes of monocular (22) and binocular (2) cases of typical optic neuritis, occurring in isolation or association with multiple sclerosis, a clearer picture of the different pattern of VEP changes in Friedreich's ataxia and optic neuritis was apparent (fig. 8).

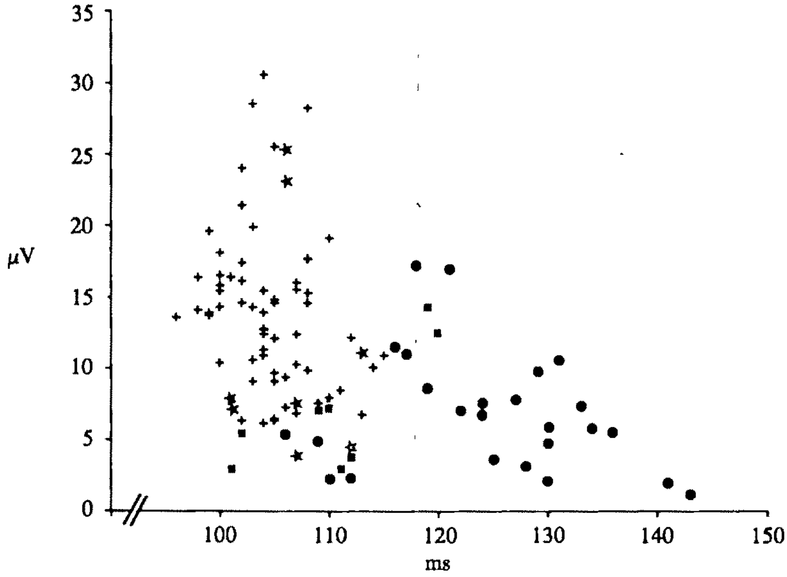

FIG. 7. P100 latency and amplitude from each eye of 31 healthy control subjects (62 eyes) and 21 patients with Friedreich's ataxia (41 eyes). The latter are divided into their three clinical neuro-ophthalmic divisions by different symbols and can be seen to cluster in two main areas on the graph. The first comprises those responses with latencies above 115 ms and which show a significant inverse relationship between the amplitude and latency (Product moment correlation coefficient, $r_{21} = 0.72$, $P < 0.001$). The second includes those responses with normal latencies but generally low amplitudes, many of which are less than 6 µV, the lowest amplitude of the healthy control subjects. Note the distribution of the clinical neuro-ophthalmic groupings within these two areas. (The open star represents the response from the previously injured eye of Case 22.) ● abnormal; ■ unknown; ★ normal; + healthy controls.

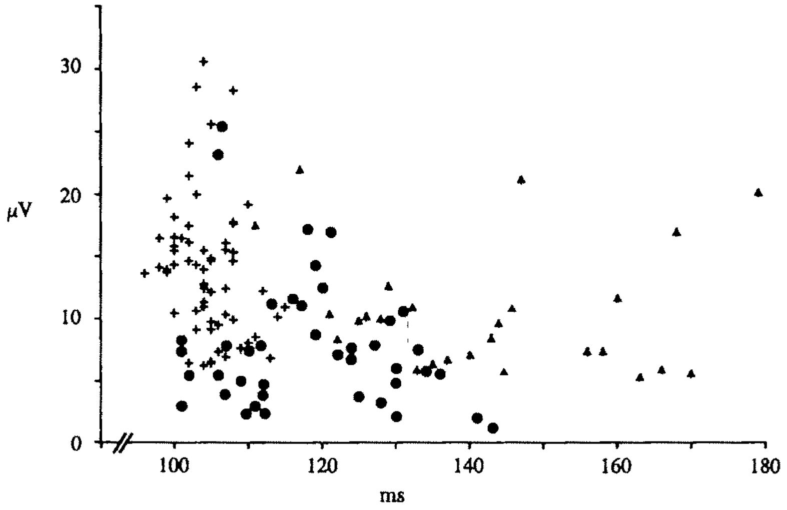

FIG. 8. Same comparison as fig. 7. The Friedreich's ataxia subjects are represented by one symbol and also included are 26 VEPs from 24 subjects who had recovered from a single typical episode of monocular (22) and binocular (2) optic neuritis occurring in isolation, or in association with multiple sclerosis. In contrast to the patients with Friedreich's ataxia the cases of optic neuritis show a clear dissociation between the P100 latency increase and the amplitude. Mean P100 latencies and amplitudes for the three groups were; 105 ms and 14.03 µV (normals), 118 ms and 7.6 µV (Friedreich's ataxia) and 142 ms and 10.4 µV (optic neuritis). + healthy controls; ● Friedreich's ataxia; ▲ optic neuritis.

Patients with optic neuritis were all matched for age, none had a visual acuity worse than 6/12 in the previously affected eye and all underwent the same VEP examination, including half-field stimulation to identify the $\overline{\mathrm{P100}}$ component. They showed no obvious amplitude change associated with the increase in $\overline{\mathrm{P100}}$ latency. In contrast, the group of patients with Friedreich's ataxia with prolonged VEP latencies showed an associated reduction in amplitude which increased with the delay. Non-parametric analysis (Mann-Whitney U tests) showed the wide-field $\overline{\mathrm{P100}}$ latency from both eyes of the Friedreich's ataxia patients to be longer than normals ($P < 0.001$) and shorter than the optic neuritis cases ($P < 0.001$ for the eye with the longer of the two latencies in each patient; $P = 0.04$ for the eye with the shorter of the two latencies). The $\overline{\mathrm{P100}}$ amplitude from both eyes of the Friedreich's ataxia patients was smaller than both the normals ($P < 0.001$) and the optic neuritis cases ($P < 0.01$).

DISCUSSION

The present study has identified a high incidence of VEP and clinical neuro-ophthalmic abnormalities in 22 cases of Friedreich's ataxia. The incidence of visual pathway involvement in Friedreich's ataxia recorded in the literature is variable and has not been well defined. Different observers have used different criteria but most have made reference to the presence of optic disc pallor or reduced visual acuity, or both. Accepting these limitations the incidence of optic atrophy in previous studies ranges from 50 per cent (18/36) reported by Geoffroy *et al.* (1976), who gave few details of how this percentage was derived, to 12 per cent of the 91 cases reported by Sjögren (1943). Pale discs or temporal disc pallor without reduction of visual acuity was noted by Bell and Carmichael (1939) in 26 per cent (15/57), whereas Andermann *et al.* (1976) found optic atrophy and poor acuity in 4 of 13 cases (30 per cent). Optic atrophy was not found in any of the 160 family members examined by Heck (1964) and 3 of the 6 cases with clinical evidence of Friedreich's ataxia who were tested with A-O pseudoisochromatic plates had normal colour vision. Friedreich (1876) ascribed the poor visual acuity to nystagmus but cited a similar case reported by Cruveilhier who had had optic atrophy confirmed at autopsy. Other references to the association of optic atrophy and Friedreich's ataxia include Hallervorden (1936), André-van Leeuwen (1949), Wilson (1954), Nayrac, Graux, François and Rabache (1957), Sylvester (1958) and Heck (1963). Reports of anatomical examination of the visual pathways in Friedreich's ataxia are few and incomplete (Cruveilhier; cited by Friedreich, 1876; Urich *et al.*, 1957; Boudin *et al.*, 1972; Oppenheimer, 1976).

Several aspects of the clinical neuro-ophthalmic findings deserve further comment. First, it is worth considering the criteria used to define the clinical abnormalities in view of their relatively subtle nature. Non-specific dyschromatopsia is a sensitive measure of optic nerve damage affecting central vision (Walsh and Hoyt, 1969) and, although the degree of impairment identified in the present series was mild, it was outside previously established normal limits in 5 of the 13 patients tested. The reduced number of small vessels crossing the disc margin found in some subjects is also thought to indicate involvement of the optic nerves. The degree of temporal pallor of the optic disc is difficult to quantify but all the assessments were made by the same examiner and, like the other clinical parameters, it was assessed before the VEP study. The association of temporal disc pallor with mild dyschromatopsia or reduced numbers of small vessels crossing the disc margin in all but Case 9 and an abnormal VEP in all but Case 13 supports the validity of the identification of this subjective ophthalmoscopic parameter. Secondly, the clinical neuro-ophthalmic abnormalities were asymptomatic. None of the 22 patients, not even the 14 with abnormal clinical findings, had noted any gradual or sudden impairment of vision. In these respects the clinical findings were similar to some cases of multiple sclerosis and some asymptomatic at risk relatives of cases with Leber's optic neuropathy (Dorfman, Nikoskelainen, Rosenthal and Sogg, 1977; Carroll and Mastaglia, 1979), both of whom can have ophthalmoscopic abnormalities and a mild but definite impairment of colour vision. Thirdly, there was no relationship between the neuro-ophthalmic abnormalities and the duration of the generalized disease, a feature also noted by Bell and Carmichael (1939). All 14 clinically abnormal patients were over 20 years of age and all had had general symptoms for more than ten years yet by comparison 3 patients with generalized disease for between nineteen and forty-one years were clinically normal. Fourthly, the most frequent clinical abnormality was mild to moderate temporal pallor of the optic disc. Although other clinical abnormalities indicated an abnormal VEP when they were found, the appearance of the disc was the most consistent and reliable predictor of the VEP result.

The finding of an abnormal VEP in 64 per cent of subjects in the present series is significant for a number of reasons. It confirms earlier brief reports of increased VEP latencies in cases of spinocerebellar degeneration (Halliday, McDonald and Mushin, 1973; Asselman, Chadwick and Marsden, 1975) and may assist the characterization of the nature of the process. In this regard Friedreich's ataxia differs from the late onset, autosomal dominant form of cerebellar cortical degeneration (Eadie, 1975). In a detailed clinical and electrophysiological study of a three generation family of 16 members with this latter condition, 4 of whom were clinically affected, no VEP abnormalities were found (W. M. Carroll, J. L. Black, L. Cala and D. W. K. Collins, unpublished observations).

Certain features of the VEP findings in the present study provide an indication of the probable pathophysiology of the visual pathway involvement in Friedreich's ataxia. The two main changes seen in the 22 subjects were a generalized reduction in amplitude and prolongation of the VEP latency, but there was no accompanying change in the waveform of the response and temporal dispersion was not a feature. This is unlike the picture encountered in some common forms of optic nerve disease (for example, compression or ischæmic optic neuropathy) (Halliday *et al.*, 1976). Another characteristic feature was the similarity of the response from the two eyes. Interocular latency and amplitude differences were within normal limits suggesting a generalized effect on the fibres in both visual pathways. Evidently the afferent volley arrives at the cortex in a relatively synchronous fashion. These features and the lack of marked temporal dispersion or waveform changes make the VEP amplitude and latency changes all the more interesting. In the absence of significant refractive error (Collins, Carroll, Black and Walsh, 1979) or lens and media opacities (A. Kriss, W. M. Carroll, G. Barrett and A. M. Halliday, unpublished observations) which degrade the pattern stimulus reaching the retina, or of significant retinal involvement, the reduced VEP amplitude presumably reflects either impaired cortical generator function or a reduction in the number of functional fibres in the visual pathway. These two alternatives cannot be distinguished by the results of this study. However, the only recent studies of the visual pathway in Friedreich's ataxia known to us (Urich *et al.*, 1957; Boudin *et al.*, 1972; Oppenheimer, 1976) support the contention that the attenuation of the response amplitude is most likely to be due to nerve fibre depletion. Brief mention of gliosis of the optic nerves, chiasm and tracts in their single case was made by Urich *et al.* (1957), and Boudin *et al.* (1972) reported similar findings in the optic tracts of one case but considered the chiasm and optic radiations to be normal. In a study of 15 cases of Friedreich's ataxia Oppenheimer (1976) found varying degrees of nerve fibre loss in the optic tracts in 'about half' and cell depletion in the lateral geniculate nucleus of the more severely affected cases but did not mention the state of the optic nerves. A recent examination of 12 of these cases confirmed the loss of myelin and nerve fibres in the optic tracts and radiations in 6 cases and in 2 the changes were severe with gliosis and cell loss in the lateral geniculate nucleus. The proximal portions of the optic nerves and the chiasm were also studied in these 2 cases and here too axon and myelin loss were present (Hughes, J. T., personal communication).

While nerve fibre loss is the probable mechanism for the reduced VEP amplitude the explanation for the VEP latency increase is, at first sight, less obvious. A delayed VEP is characteristic of demyelinating optic neuropathy (Halliday and McDonald, 1977). The VEP latencies and amplitudes of the age and acuity-matched cases of typical optic neuritis included in fig. 8 demonstrate the combination of prolonged latency and normal amplitude so characteristic of this form of optic neuropathy. By comparison, those Friedreich's ataxia subjects with increased VEP latencies show a highly significant inverse relationship between the latency and amplitude. This particular combination of VEP changes suggests that the pathological process in Friedreich's ataxia differs from that occurring in demyelinating optic neuropathy and that the same mechanism is likely to underly both the amplitude attenuation and latency prolongation in this condition. There are several possible explanations for the VEP latency increase. These include fibre shrinkage and/or paranodal demyelination associated with axonal degeneration, drop out of large fibres leaving the smaller, more slowly conducting axons to initiate the response, reduced efficiency of transynaptic transmission due to decreased fibre terminals, and impaired membrane function (nodal and/or synaptic). Functional impairment of the nerve membrane has been invoked to explain slowing of conduction without histological changes in the peripheral nervous system (Behse and Buchthal, 1978) but the mechanism for this is unknown. In a disease with such widespread and multi-system effects like Friedreich's ataxia this type of abnormality cannot be readily excluded. The effect of reduced numbers of fibre terminals on visual pathway transynaptic transmission is unknown, but this seems unlikely to account for the degree of slowing of conduction found in the present study. The remaining possible causes of increased conduction time are all known to occur in the peripheral nervous system and reports of nerve fibre loss in the visual pathway are cited above. Loss of the faster conducting fibres alone would seem the least probable cause as nearly all the fibres in the optic nerve are less than 3 μm in diameter (Chacko, 1948) and they are all the same length. Although fibre shrinkage and associated secondary paranodal demyelination have not been observed in the visual pathways, these changes may well be a significant factor in prolonging the VEP latency.

There are two further points worthy of brief note. First, what is happening to those Friedreich's ataxia patients with low amplitude responses and normal latencies? They may represent one or more possibilities, such as a different process, a more selective process causing conduction block without slowing, or the same process as the other group with increased latencies but whose latency increment is not apparent in a single study. Further serial examinations of these and other cases are needed to resolve this question. Secondly, although the study involved only one examination the relation between the $\overline{\mathrm{P100}}$ amplitude and the disease duration suggested a continuing process. While it might be argued that this trend occurred because of the close association between visual acuity and $\overline{\mathrm{P100}}$ amplitude (fig. 5), these two parameters probably reflect the same pathophysiological process. If so, the $\overline{\mathrm{P100}}$ amplitude was a more sensitive index in this regard as there was no correlation between the visual acuity and the disease duration.

Thus, the VEP findings suggest a progressive nerve fibre loss in the visual pathway with associated slowing of conduction. These findings are consistent with the histological observations in the peripheral nervous system (Hughes *et al.*, 1968; Dyck and Lais, 1973) and visual pathways (Urich *et al.*, 1957; Boudin *et al.*, 1972; Oppenheimer, 1976; Hughes, J. T., personal communication, 1979) and with the more detailed and accurate electrophysiological studies in the peripheral nervous system (Dyck *et al.*, 1971; MacKenzie, Skuse and Lethlean, 1977). Slowing of conduction has also been identified in the central somatosensory pathway (Desmedt and Noel, 1973; Sauer and Schenck, 1977; Mastaglia, Black, Edis and Collins, 1978; Jones, Baraitser and Halliday, 1980). Indeed, in the somatosensory pathway study of Jones *et al.* (1980) on the same 22 patients, the latency of the primary response at the cortex ($\overline{\mathrm{N20}}$) was increased by between 4.0 ms and 25.3 ms (mean 14.4 ms) which compared closely to the present study where the mean $\overline{\mathrm{P100}}$ latency was increased by 13 ms (range 1 to 38 ms) compared to the mean $\overline{\mathrm{P100}}$

latency from normals. The marked temporal dispersion of the $\overline{\mathrm{N20}}$ component was, however, a major difference between the findings of the two studies although this is probably due to differences in the genesis of the $\overline{\mathrm{N20}}$ and $\overline{\mathrm{P100}}$ components and the disparate range of fibre diameters in the two systems. Nevertheless, the latency increments found in these two central pathways, which are of similar length, may reflect a limit to the degree of conduction slowing which can occur with this particular pathophysiological process before conduction block supervenes. It is interesting to note also that it was those patients with recognizable temporal disc pallor that had an abnormally prolonged VEP latency or an absent response. Might this indicate that the 'dying back' of the degenerating axons was more severe in these cases, extending back towards the retinal ganglion cells? The mildly abnormal ERG recordings from three patients with abnormal clinical neuro-ophthalmic and VEP findings are in agreement with this possibility.

In conclusion the results of this study show that the visual pathway is frequently and asymptomatically affected in Friedreich's ataxia. In addition, the nature of the VEP changes are consistent with the same process of axonal degeneration found throughout the nervous system in this condition and indicate that slowing of conduction is a major feature in the visual pathway.

SUMMARY

Pattern-reversal visual evoked potentials (VEP) were recorded from 22 patients (mean age 33.7 years) with Friedreich's ataxia, 15 of whom also had a detailed neuro-ophthalmological assessment prior to the VEP examination. None had noted symptomatic visual impairment. Eleven of the 15 (73 per cent) examined clinically had one or more neuro-ophthalmic abnormality and 14/22 (64 per cent) had an abnormal VEP study which was always binocular and comprised absent responses, or most commonly, increased $\overline{\mathrm{P100}}$ component latencies. The maximum $\overline{\mathrm{P100}}$ latency was 143 ms and the group mean was 118 ms. The $\overline{\mathrm{P100}}$ amplitude was also generally reduced particularly in those patients with latencies less than 115 ms (upper limit of normal), while in those with latencies above the normal range there was a significant inverse correlation between the $\overline{\mathrm{P100}}$ amplitude and latency. The waveform, temporal dispersion and interocular differences were normal in almost all patients with identifiable responses, including those with prolonged VEP latencies. Electroretinograms recorded from three selected patients were either normal or minimally abnormal and suggested secondary rather than primary retinal involvement. The only VEP parameter to correlate with either the duration of the generalized disease or the visual acuity was the $\overline{\mathrm{P100}}$ amplitude. A good correlation was found between the VEP and the clinical neuro-ophthalmic findings. Temporal pallor of the optic disc was most often associated with an abnormal VEP result and impaired visual acuity or colour vision were uncommon in the absence of VEP abnormalities.

The VEP changes and those obtained from 24 age- and acuity-matched cases of demyelinating optic neuritis are contrasted and the probable pathophysiology is discussed. Two main conclusions emerge from this study. First, there is a high incidence of asymptomatic visual pathway involvement in Friedreich's ataxia which can be demonstrated by both clinical and VEP examination. Secondly, the VEP changes in Friedreich's ataxia differ from those found in typical demyelinating optic neuropathy and are consistent with progressive nerve fibre loss and associated slowing of conduction, indicating that the visual pathway is affected by the same widespread process of axonal degeneration found throughout the nervous system.

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NOTICES OF RECENT PUBLICATIONS

Mammalian Vestibular Physiology. By V. J. WILSON and G. MELVILL JONES. 1979. Pp. 340. Price $32.50.

Neuronal Operations in the Vestibular System. By W. PRECHT. Studies of Brain Function. 1978. Pp. 223. Berlin: Springer. Price DM 43.00.

Clinical Neurophysiology of the Vestibular System. By R. W. BALOH and V. HONRUBIA. Contemporary Neurology Series. 1979. Pp. 230. Philadelphia: F. H. Davis. Price $37.50.

Vestibular Mechanisms in Health and Disease. Edited by J. D. HOOD. 1978. Pp. 378. London and New York: Academic Press. Price £13·80.

Advances in the neurosensory physiology of the vestibular system have never been as spectacular as in the other special senses, particularly vision. Although the roots of vestibular physiology go back more than a hundred years to Flourens, and its important role in the regulation of posture was well established early in this century by such people as Magnus, the vestibular system until recently was not really a central topic in neurophysiology and remained the area of a few specialists. Much of the work on the system was done—ever since Bárány—in a clinical context, or inspired by the practical problems of advanced means of transportation such as aircraft and space flight. Nystagmus, dizziness and motion sickness were the central issues, and—mainly to study pathology—such methods as caloric and rotatory stimulation, and electronystagmography, were developed by clinicians. The mechanics of the peripheral sense organ on the other hand has aroused the interest of physicists since the time of Mach, and a valid mathematical model of the movement of the cupula was developed by Steinhausen in 1933. Most of the early fundamental work on the labyrinth was done on fishes, where the organ is more accessible than in mammals. In the latter, vestibular physiology was mainly investigated indirectly through the effects of lesions or the properties of vestibular reflexes, especially the vestibulo-ocular system. For several decades, physicists and physicians had to fill the gap in neurophysiological knowledge by largely ignoring the nervous system, or at least assuming very straightforward connections between vestibular afferents and motor neurons. Thus, it was attempted for many years to derive the parameters of Steinhausen's equations for cupular motion directly from the dynamics of vestibulo-ocular reflexes or motion sensations, and secondary after-nystagmus was explained by an overshoot of the cupula, even though such an assumption bluntly violated Steinhausen's model.

Particularly in the last decade, neurophysiologists have finally stepped in and provided a large body of knowledge of the generation and particularly the central processing of vestibular signals. The informational content of this signal flow is admittedly less rich and exciting than that of vision or hearing, after all, the vestibular organs are traditionally described as proprioceptive. On the other hand, these signals are more readily interpretable and suitable for analytical description and so are the reflex systems in which they function. Some of the major advances in the field may be specifically mentioned here.

Direct recordings have been realized from the afferent fibres of the ampullæ and maculæ in monkey, cat and frog and the responses to a wide range of stimuli has been recorded. Even at this level, the signalling of the mechanical excursions of cupula and otoliths is complicated by adaptation and rate sensitivity of the hair cells. In the last few years also the latter have been penetrated and the mechanoneural transduction process has been directly studied.

Single unit recording in the vestibular nuclei has revealed complex processing of motion signals, with intricate commissural connections. These units carry, in addition to vestibular signals, visual motion and even oculomotor signals. Optokinetic nystagmus and after-nystagmus as well as vestibular nystagmus are represented in the vestibular nuclei, and bilateral loss of the labyrinths degrades optokinetic nystagmus. Clearly, visual and vestibular control of postural reactions are highly integrated at this level. Clinicians may have understood this intuitively, since optokinetic nystagmus has been investigated routinely along with vestibular functions for many years. Many of these findings were only possible by the development of single unit recording techniques in behaviourally alert animals.

The synaptic connections of the afferent and efferent vestibular nuclear fibres to the oculomotor nuclei, spinal cord, cerebellum, reticular formation and other centres have been studied in great detail. The development of vestibular physiology is strongly related to the progress in oculomotor physiology and both have greatly profited from the modern modelling approach in which hypotheses are stated in the form of diagrams and equations and activities are interpretated as signals.

The vestibular system is highly suitable for much modelling, since its functions and signals can be rather unambiguously defined. However, even this relatively simple system is not a rigid control system: it can learn. Its transfer characteristics show a very meaningful adaptation to altered conditions, for instance, a changed relation between head movements and retinal image shifts caused by magnifying, reducing or even inverting spectacles. The cerebellum, with which the vestibular system is strongly connected, is probably instrumental in this plasticity and a fruitful symbiosis has now developed between vestibular and cerebellar research.

The increased interest in vestibular physiology is reflected in the appearance of many new publications, among which are the four books to be reviewed here. They are quite different in character and aimed at different readerships.

Mammalian Vestibular Physiology by V. J. Wilson and G. Melvill Jones will undoubtedly appeal to a broad public. It is an excellent and profound overview of the vestibular system. The authors are not only leading investigators but also very good writers, who, as a couple, clearly complement each other's special expertise in some subfields. They succeed in presenting a complete, balanced and critical account that is equally interesting as an introduction and as a source book for the specialist. The text is very readable and reviews the important evidence intelligently, fairly and coherently. It is educated without pedantry, complete without confusing detail, authoritative in the best sense. Everyone with a serious interest in the vestibular system should have this book handy to know the state of the art. The book contains chapters on peripheral morphology, biophysics of the peripheral end organs, mechanoneural transduction and primary afferent response, input to vestibular nuclei and reticular formation, the relation to the cerebellum, the vestibulospinal system and the vestibulo-ocular system. Since no book review is complete without some criticism, I shall mention a few minor ones. In the discussion of the action of linear acceleration on the canal a role of cupula-endolymph density differences is considered unlikely as the basis of Money's measurements in pigeons. I missed a comment on Money's later experiments in which the ingestion of alcohol and heavy water was shown to cause positional nystagmus in opposite directions, presumably due to differential absorption and excretion rates in cupula and endolymph. Ter Braak once calculated that extremely small density differences should be sufficient to make the canal susceptible to linear accelerations. Maybe the possibility for such differences to occur *in vivo*, and *a fortiori* in pathology, should be re-investigated. In the discussion on mechanoneural transduction I regretted finding no reference to the beautiful results of Hudspeth with intracellular recording from macular hair cells. The discussion of postrotatory nystagmus is rather short and also difficult to find, even with the index, which might be enlarged as it has no entries for such common terms as acceleration, after-nystagmus, plasticity or habituation.

Neuronal Operations in the Vestibular System by W. Precht is a quite different text. It appeared in Studies of Brain Function, a series of monographs which offer a forum to neurobiologists to comprehensively describe the investigations that they have performed over a number of years on a system, which may have been published in a number of papers distributed over different journals, books and proceedings. It seems an attractive opportunity for both author and readers to systematically review a body of work with the possibility of putting the findings in the new perspectives offered by the progress of the author's own investigations and the field in general. Anyone familiar with vestibular neurophysiology will know Precht's skilful and reliable contributions that more than justify this monograph, which centres on the work he did in the last ten years, in collaboration with a group of distinguished colleagues such as Shimazu, Llinás, Baker, Berthoz and many others. In many respects this monograph is a tribute to the invisible college formed by a group of laboratories that have collaborated intensively and contributed a widely acknowledged body of reliable and coherent knowledge. While many other groups have concentrated on primates, Precht and his colleagues complement this with systematic investigations of the frog and the cat. This book is a synopsis of some 50 major publications, discussed in the context of some 250 related articles from other groups. These proportions are probably quite representative of the weight of the contributions by Precht and his colleagues to his special subfield, which is quite severely restricted to neurophysiology *pur sang*. The evidence presented consists of action potential frequencies, synaptic potentials, latencies and conduction times, excitation and inhibition; it is a no-nonsense approach of single unit responses to precisely defined planes. One cannot but admire the skill, patience and determination that have been invested in the collection of all these data which are the necessary ingredients for our understanding of the system. The book is divided into four main sections: primary vestibular neurons, central vestibular neurons, vestibulocerebellar relationship and vestibulo-ocular relationship. They are clearly and systematically written and amply demonstrate the proficiency of the author in enriching our knowledge in each of these areas. Precht provides us with a detailed network of connections from the hair cells up to the oculomotor neurons, inclusive the vestibulocerebellar loop. The emphasis is on data collection and classification, not on modelling, hypothesizing and speculation. It is a book not so much for the reader with a general interest in the system as for the real professional, to whom it will be an invaluable sourcebook.

Quite different again is *Clinical Neurophysiology of the Vestibular System* by R. W. Baloh and V. Honrubia, which appears in the Contemporary Neurology Series. This text is mainly written for the clinician, but the first 100 pages (half the book) are devoted to a gallant attempt to review the physiology of the vestibular system, including postural reflexes. As such it is a fair introduction which deals with many aspects of the system and gives extensive references to the literature, some of them quite recent, others outdated. The review gives a bit of everything; anatomy, comparative anatomy, biophysics, neurophysiology and systems analysis, but the quality is mixed and lacks the homogeneity and depth of Wilson and Jones' review, which will probably be preferred by those with a serious interest in the basic aspects of the system. Sometimes dubious or erroneous statements are made. For instance, it is suggested (p. 13) that the otolith organs respond poorly to sinusoidal stimuli above 0.5 Hz, and that the sensitivity of the semicircular canals is minimal at frequencies above 5 to 10 Hz. These assertions are certainly not consistent with the response characteristics of primary afferent fibres determined by Fernandez and Goldberg, who are quoted on pp. 41–42, where the same erroneous interpretation is repeated. The discussion of cupular mechanics largely neglects phase relations and, for instance, does not point out that with a cupular time constant of about 4 s the afferent velocity signal at 0.04 Hz will lead the stimulus velocity by about 45 deg and gain will be down to about 70 per cent. In this respect the clinical preference for testing the vestibular reflexes at a frequency of 0.05 Hz is hard to understand, since this is exactly the range where the canals cease to faithfully signal the head velocity, and ocular stabilization is very much controlled by vision. This point is mentioned on pp. 79–80, where a model is shown for visuovestibular interaction, but it may not be clear to many readers why fixed gains of 0.4 are assumed for the vestibulo-ocular reflex and 0.95 for visual control (smooth pursuit). These conditions may apply at 0.05 Hz but certainly not at higher frequencies, and it may be asked what the explanatory value of such diagrams as fig. 41 is for the understanding of such a complex subject as visuovestibular interaction. The description of tonic labyrinthine reflexes (p. 85) is erroneous. It is stated that upward tilt of the head increases tone in the forelegs, and that lateral tilt produces extension of the extremities on the other side. This would be very strange since it would reinforce rather than compensate the head deviations, and in reality these reflexes work of course the other way around, as described very clearly in the monograph by Roberts, *Neurophysiology of Postural Mechanisms*, which figures in the list of references.

The clinical part offers a review of current methods of investigation and differential diagnosis of vestibular system disease. The significance of a 5-page chapter on clinical evaluation of hearing is probably minimal, but the rest of this part seems a useful introduction for clinicians with an interest in this system. The quality—as far I can judge it—seems somewhat mixed again. To illustrate, some recent results of Zee *et al.* on cerebellar ataxia and ocular motor apraxia (published in *Brain*) are quoted but the interesting findings of the same author on abnormalities of optokinetic nystagmus due to labyrinthine defects (published in *Brain Research*) are not mentioned. The studies of Money and Myles (1974) on positional nystagmus are quoted (p. 203), but unfortunately the formula of heavy water is given as H_3O instead of D_2O.

Vestibular Mechanisms in Health and Disease contains the Proceedings of the Sixth Extraordinary Meeting of the Bárány Society, held in London in September 1977, and edited by J. D. Hood. Conference proceedings are being published in abundance, often even with some automatism, and obviously the quality and character varies a great deal. In most cases the material is not unique, since most of it has been or will be published as articles in the various journals. This element of redundancy in itself is not necessarily bad, since a representative collection of recent work can provide an excellent overview of the state of the art to a field. To be most useful, conference—as well as its proceedings—should concentrate on a well defined theme, it should represent the best work in the field, and it should show something of its structure; some perspectives of past, present and future developments, and of the interaction between the different groups. In short, the reader should get a good feeling of what important things are going on in the field. Judged by such criteria, the contribution of the present book is not very important. The contents are very heterogeneous in subject and level. Four main themes (problems of head stability, central control of vestibulo-oculomotor functions, positional nystagmus, and signal processing in the evaluation of vestibular mechanisms) were planned, which seems more than enough, but in addition a large number of free papers on almost every aspect of vestibular function was included. As a result the contents fall into no less than ten sections, and are probably more determined by the fortuitous composition of the audience than by a rigorous selection process. Most papers are short and restricted to the presentation of recent results. There are no major reviews, discussions or workshops to improve the coherence. About one-third of the papers is on patient material, the rest is experimental. The neurophysiology section contains a number of good papers, but practically all of them have been published more extensively elsewhere. In the computer analysis section one finds interesting material on nystagmus analysis, for example by Young and Tole, and an interesting new analysis method, a pseudorandom binary sequence of accelerations, is presented in several papers by O'Leary, Peterka and associates. The section on positional nystagmus is interesting but also shows that there is little advance in the understanding of the basic mechanisms. The role of otolith organs or semicircular canals (e.g. by a change in density of the cupula due to pathological processes) is still much in doubt. What seems to be needed is a good animal model of positional nystagmus with electrophysiological recordings from identified primary afferents and secondary neurons. As a whole, this book is too haphazard in composition and level to be recommended as an authoritative reference book.

H. COLLEWIJN

Progress in Clinical Neurophysiology. Edited by J. E. DESMEDT. 1978. Basel: Karger. Vol. 4. **Cerebral Motor Control in Man: Long Loop Mechanisms.** Pp. 392. Price DM 141.00. Vol. 5. **Physiological Tremor, Pathological Tremors and Clonus.** Pp. 218. Price DM 117.00.

These two volumes contain articles based on a symposium held in 1976. This was organized by Professor J. Desmedt, who once again has successfully encouraged a group of distinguished neuroscientists to contribute much extended versions of the papers they had originally presented. The result is that both books contain well written and balanced articles, up-to-date and well tempered by symposium discussion.

Cerebral Motor Control in Man. As Phillips observes in his introductory chapter on Background and General concepts, much of the experimental work described in this volume deals with the attempt to establish the existence of 'long loop reflexes', the topic which forms the sub-title of this volume. In the present context the concept of 'long loop reflexes' has its origins in Phillips' (1969) Ferrier Lecture in which he suggests that the well-known segmental servo loop has been supplemented or even supplanted by a transcortical loop, with a loop time shorter than the earliest voluntary response to brief mechanical stimulation of a moving limb, i.e. a kinæsthetic reaction time. The importance of such reflexes is thought to lie in the automatic compensation they provide for unexpected variations in mechanical load during voluntary movement. This seemingly simple proposition conceals a problem of considerable complexity, whose epistemological roots require some exposure if the reader is to understand the scope of this important book.

Having regard for the fact that the primate cortico-motoneuronal (CM) tract is a rapidly conducting system of fibres, directly coupling the motor cortex to the spinal motoneurons, Phillips had stated in relation to experiments involving suddenly obstructed movement of the primate limbs: 'One may hazard the speculation that the increased discharge of the PT cell (pyramidal tract neuron) . . . was in response to a signal of mismatch between "intended" and actual displacement. Whether this signal is a crude one from the muscle spindles, or whether the mismatch has been computed by the cerebellum is still unknown; nor in this experiment, can the contributions of joint, skin and vision be assessed. But however "instructed" the CM projection would transfer the "instruction" for increased force to the motoneurone with maximum directness.'

The use of the terms 'intended' and 'mismatch', coupled with Phillips' description 'transcortical servo', form part of the terminology of the 'length' and 'length follow-up' servo theory of Merton (1951) for which the mismatch signal is the muscle spindle afferent discharge. A key feature of Merton's theory was the insentient mode of operation of the servo mechanism. It was then held that spindle afferents do not project to the cerebral cortex, and hence into consciousness, which thus allowed a phase of reflex, i.e. not dependent on consciousness *per se*, load compensation to occur in normal conscious man without the need to implicate a voluntary response to the *perceived* load. The idea that 'intended' (voluntary) movement could be automatically regulated through a spindle dependent mechanism, whose functional operation is not perceived remains an implicit, if not explicit, feature of the 'long loop' reflexes. Indeed, this determines the very design of the experiments aimed at distinguishing between voluntary and reflex.

Whereas voluntary reaction times to auditory and visual stimulation are typically much longer than to kinæsthetic stimuli, a fundamental problem exists in distinguishing between kinæsthetic reaction times and the earlier, reflex actions which the same stimulus evokes. This is the field of enquiry principally exercizing the minds of those contributing to this book; their endeavours are expressed both in terms of fundamental research and in studies directed towards a better understanding of movement pathophysiology in man and animals. Work by Evarts and Vaughn deals specifically with the problem of kinæsthesia and it leads specifically to the important general conclusion that the response to a kinæsthetic stimulus, involving muscle stretch, consists of three phases of action: (1) a spinal reflex; (2) a longer latency reflex traversing the motor cortex and pyramidal tract; (3) an 'intended' response whose latency represents the kinæsthetic reaction time. Recorded electromyographically, this reaction time has a minimum value of 70 ms; it should be recognized that this is substantially shorter than the minimum value of 100 ms commonly assigned for voluntary reaction times to purely cutaneous stimuli applied in the absence of limb movement, or to auditory or visual stimuli. These conclusions are essentially the same as those reached by Marsden, Merton and Morton in related experiments on the thumb flexors. However, readers will become aware that some caution has to be exercized in comparing the responses of different muscles to stretch, because of the likely differing contributions of segmental and long loop mechanisms, especially in relation to the antigravity muscles.

In this regard, only Houk gives serious consideration of the views of the Lundberg School (and of the present author) that the long latency responses could as much represent supraspinally mediated control of transmission in segmental reflex arcs as the encephalization of the stretch reflex, with its implied specific involvement of the spindle 'error' signal. Be this as it may, any serious student of the control of human movement will find this book an important statement of the present state of the subject and only price is likely to inhibit its purchase.

Physiological Tremor, Pathological Tremors and Clonus. For the author, the contents of this book on tremor provide a welcome change from the kinds of article published some years ago, in which authors seemed always intent on finding an exclusive mechanism, 'central' or 'peripheral' (often referred to as peripheral in this field of work) to account for the particular tremor under consideration. In part, such preoccupation arose from the central role which the segmental stretch reflex mechanism was held to play in the control of movement. However, as will be understood from the outline given above of the more fashionable long loop mechanisms, the picture is now infinitely more complicated, and the various authors have wisely refrained from such dogmatism when discussing their results. However, this has not led to indecisive accounts. To the contrary, with few exceptions the authors have achieved an excellent balance between didactic, theoretical, and speculative considerations in presenting their points of view, the consequence being that this difficult subject of tremor is dealt with most comprehensively. For the prospective reader, one cannot help but single out the excellent introductory chapter by Marsden, which successfully filters out all but the key papers and issues; while that of Rack's provides one of the clearest statements I have read of the fundamental problems involved in the interaction between mechanical and reflex factors, when tremor is investigated by altering the mechanical load. Freund and Dietz provide a comprehensive account of their extensive investigation of the relations between physiological and pathological tremor, based on force and EMG measurements of single units, and this chapter complements in particular the one by Rondot and collaborators based on more global electromyography.

The paper by Wallin and Hagbarth is of particular importance, because, using the technique of microneuronography they provide direct evidence for the firing behaviour of muscle spindles during tremor. Thus they have demonstrated that not only does alpha-gamma coactivation occur during rapid, tremor-like alternating finger or foot movements, but such alpha-gamma linkage is retained in Parkinsonism, which leads then to conclude that the essential motor deficit is the abnormal release of programmes for motor behaviour normally used for purposeful contractions. In contrast, during clonus, the spindles are silent during the active phase of contraction, being excited only during the relaxation extension provided by the myograph spring. This result is of considerable importance because it explains why, to evoke sustained clonus, the examiner needs to apply a sustained stretching force to the relevent muscle, thus directly confirming the same conclusion reached by Dimitrijevic, Sherwood and Nathan, based on their studies of the knee jerk as described in a later chapter. These papers are referred to simply to illustrate the important topics covered in this book, which should be of interest and value to clinical neurologists and neurophysiologists seeking an up-to-date account of present methods and concepts in this field.

T. A. SEARS

Severe Accidental Head Injury by A. H. ROBERTS. 1979. Pp. 226. London: Macmillan. Price £14·00.

The last ten years has seen an upsurge in interest in the outcome of severely head-injured patients, together with concern about the quality of life of some of those who now survive injuries which would previously have been fatal. This report of an investigation into the degree of disability ten to twenty-five years after severe head injury, by a neurologist, a psychologist and a social worker, has therefore been eagerly anticipated. They are to be congratulated for the diligence and persistence which enabled them to trace all but a handful of the more than 500 patients whom they set out to follow. Most of the short-fall had died and details of the cause of death were obtained for these. There is substance in the author's claim that these 300 patients represent the largest such study—although his review of the literature shows that there have been many previous series of some size.

Perhaps the most interesting chapters, because they are the most factual and least controversial, are those dealing with cranial nerve disorders, pituitary and hypothalamic dysfunction, epilepsy and late systemic complications. The author writes with particular authority on post-traumatic dementia of a progressive kind, in view of his previous work on boxers' brains. He concludes that a single serious head injury seldom initiates a process of progressive encephalopathy, but that there is some evidence that brain-damaged patients may age prematurely. The data on life expectancy are of considerable medico-legal importance, and are based on a sizeable number of patients followed to death. There was a significant increase in death from meningitis, epilepsy and accidental drowning; although deaths from suicide and from second accidents were each three times more common than in an age-matched population without head injury, this difference was not statistically significant. The life expectancy of those able to leave hospital was reduced by only about five years, over the next twenty years.

The central chapters are those dealing with mental disability and what is termed 'central neural disability'. Four patterns of physical handicap were recognized—decerebrate dementia, athetoid pseudobulbar, brain-stem cerebellar and hemiparetic. Mental disorders were classified into many syndromes using terms that are neither readily recognized nor precisely described (e.g. fronto-limbic dementia, phobic imbalance, dysmnesic inadequacy, frontal dysmnesia, and schizophreniform psychosis). Graphs purporting to show the balance between personality and intellectual disorders in 12 such syndromes are so poorly reproduced as to be illegible without a magnifying glass. The findings of psychometry are described in some detail, and the choice of tests seems to have been sensible. However, there is a reference to 'WAIS Designs', indicating a confusion between the block design subtest of the WAIS and the visual reproduction of the Wechsler Memory Scale. Many of the tests appear to have been performed only on a subset of less severely right-handed men, and it cannot be presumed that these findings apply to the series as a whole. Much is made of the difference between the cognitive disorders in patients with impacts on the right and left sides of the head, respectively; however, re-analysis shows that a significant difference applies only to the parieto-occipital impacts, and those with left-sided impacts in this region were on average ten years older than the right-sided impacts. As some of the groups are only of 2, 4 and 7 patients the data in this chapter are at best unconvincing.

Both mental and physical disability are scored on an eleven-point scale, which includes severe, profound and total disability as three separate categories; and there are two degrees of disability worse than 'total'. No clear definitions are given of the disabilities which 'preclude', 'limit substantially', cause 'difficulties', or 'inconvenience', or are of 'little significance' in domestic, social or occupational life; yet these are the terms used to describe neural responsiveness or state of consciousness. Moreover they are used not only to describe late disability but also the patient's state in the acute period—which seems inappropriate. Although there is an analysis to show the overall predominance of mental deficit over physical in reducing occupational status in all but unskilled workers, there is no attempt to relate the different mental and cognitive disorders to the physical syndromes in the same patients. Nor is there any indication how the disability scale relates to the Glasgow Outcome Scale, which has been used in most head injury publications from North America and Europe in the last three or four years. (Jennett and Bond, 1975; Langfitt, 1978).

This is not the only feature which makes it difficult to compare this series of patients with others, or to apply these findings in a practical manner as a basis for decision-making in the future. All the tables which correlate disability with age and early features of injury (coma, PTA, complications) deal separately with two sets of patients. One is a consecutive series of 291 admissions to Oxford, and the other a selected series of 64 cases from various sources, with severe injuries (more than a month in coma). But 24 of the selected series are also in the consecutive series; as they are not separately identified it is impossible either to compare the consecutive with the selective series, or to add the two together to achieve bigger numbers in some of the smaller groups of interest.

Much is made of the consecutive series being representative of an unselected group of all severe injuries admitted to a single hospital. In fact the series excluded all deaths within a week, and all cases with a lucid interval; this no doubt accounts for the very low incidence of intracranial hæmatoma (17 per cent); over half the survivors of severe head injury in an international series of 1000 head injuries had a hæmatoma (Jennett, Teasdale, Braakman, Minderhoud, Heiden and Kurze (1979)). Moreover these hæmatoma cases are not separately identified but are included in a group termed 'complicated', which appears to include all cases of compound depressed fracture and also those in whom operative procedures led to 'penetration of the dura'. The claim that the severity of the series as a whole is 'in general substantially greater for a larger proportion than in previously reported series' is not well-founded. The criterion of severity was more than one week in coma, or in PTA; 34 per cent of cases had more than a month of amnesia, compared with 59 per cent for 486 survivors in the International Severe Head Injury Study (Jennett *et al.*, 1979). It is stated that data about the acute stage was taken from 'uniformly well-documented records from neurosurgical units interested in head injury'. However, details of ten illustrative cases in the appendix indicates that there was no uniformity of terminology for describing the acute stage. Old-fashioned terms such as 'lighter', 'deeper', 'responding to pain', 'presumably decerebrate', 'semi-conscious', 'moving spontaneously or purposely' abound—as was the custom before more formal and generally agreed ways of describing patients in coma were introduced in the 1970s (Teasdale, Knill-Jones and Van der Sande, 1978).

The lack of clearly defined descriptions either of initial severity or of ultimate outcome greatly limits the value of the chapter on predictions. In any event the conclusions reached, for all the display of figures, are no more than generalizations based on duration of PTA and decerebration, and on age. Even this is not always clearly defined—what are 'young adults', and when is 'middle age'? Predictions are not expressed in mathematical terms but rather that few or most of a given group are disabled, or that disabilities are usual, or seldom occur. The author's conclusion is that these indices of long-term outcome provide 'an overall guide but do not take account of individual variability'. However, doctors at the bedside are always concerned with individual patients. What was hoped for in this study was reliable information about how the rate of recovery over the first year or so might indicate the likelihood of further recovery. It does not seem, however, that detailed recovery curves were constructed, although there are some diagrams and one table to suggest the pattern of recovery. From these it would seem that of those who had made a satisfactory recovery at ten years, 87 per cent were already well recovered within six months of injury and 94 per cent by one year; and of those recovered at one year, 93 per cent were already so by six months. This is in close agreement with the figures published from the International Study.

In the light of these findings it is difficult to know how the author reached the conclusion that 'despite apparently *profound* degrees of impaired neurological dysfunction in the *acute* stage, long-term outlook is *good* (given time) . . . poor neurological or mental prognosis should not be assumed within three or perhaps even five years of injury'. Given that there are a few patients who do have potential for good recovery, even if still badly disabled some months after injury, it would be helpful to know whether these workers discovered ways of recognizing such patients.

It seems that a third of the patients were totally, severely or profoundly disabled a year after injury, and that the fall in this proportion to 27 per cent by ten years was mostly because disabled patients had died, rather than that they had recovered. In mathematical terms the author may therefore be justified in stating that 'for the *majority* of patients almost any therapeutic effort will be worthwhile, since in *general* the outlook for *at least acceptable or tolerable* domestic, social and occupational rehabilitation is *good*' (my italics). But how much use is that statement to the clinician or the family faced with a severely disabled patient three months after injury? No more helpful than another of the author's conclusions: 'Most striking factor is how *relatively uncommonly* severe physical disability persisted in the long-term, and how even incapacitating mental disability *usually* only persists with *any frequency* among the *most severely* injured'. What the decision-maker at the bedside wants to know, week by week and month by month, is exactly how the odds against the attainment of certain clearly defined degrees of recovery are altering in that individual patient. To give relatives unrealistic hopes for recovery is at best unkind, and at worst dishonest; and to expend resources on elaborate treatment when this cannot be effective is unfair to other patients who do have potential for recovery but who are thereby deprived of facilities. (Jennett, 1976).

These two chapters make two particular propositions about the mechanism and location of the brain damage responsible for residual disability. There is a very involved discussion which attempts to relate the pathological lesions to some of the clinical findings, and draws parallels with the author's previous studies on boxers' brains. As the present study has no pathological component, and does not take proper account of neuropathological findings and opinions published in several places in the last five years or so, this is a rather unsatisfactory and speculative section of the book. It is no doubt true that secondary events, in particular hypoxic brain damage, do account for some of the persisting handicaps. But the evidence adduced in support of this concept is dubious, in the light of recent neuropathological work. The author argues that prolonged coma without a skull facture is likely to indicate secondary rather than primary brain damage. This is completely contrary to pathological evidence published in this Journal that diffuse white matter damage sustained at impact is characterized by a low incidence of skull fracture and always accompanied by prolonged coma (Adams, Mitchell, Graham and Doyle, 1977). It seems likely, therefore, that the cases which the author considers to have secondary brain damage are those in whom severe primary brain damage is more probable.

An argument is also advanced that blows on one side of the head are commonly associated with contrecoup brain damage. Great emphasis is placed on the site of the skull fracture as evidence for this, but no more than a passing reference is made to evidence about the relationship of this to underlying brain damage. In fact both pathological analysis on a systematic scale (Adams, Scott, Parker, Graham and Doyle, 1980), and careful study of large numbers of CT scans after recent and remote trauma, make it doubtful whether contrecoup brain damage is anything like as frequent as has been supposed. The majority of patients of the kind described in this book have bilateral brain damage; the most suitable cases for studying localized brain damage would have been those who developed intracranial hæmatoma after a lucid interval (indicating lack of severe impact damage). Unfortunately such cases were specifically excluded from this study.

References to recent work in the fields of neuropsychology of head injury, and of rehabilitation after head injury are also curiously deficient—and the impression is that the review of the literature was completed several years ago, with only a few token additions since then. This book therefore stands as a landmark of the state of knowledge a decade ago; indeed many of the patients studied were treated twenty-five to thirty years ago. Although many problems remain to be solved, there are now many serious studies being conducted prospectively in several countries which promise to advance our understanding of the process of recovery after severe head injury. A gratifying feature of this newly kindled concern about head injury is that many workers are using similar means of assessment, both in the acute stage and during recovery (Langfitt, 1978). There is a prospect therefore of sufficient experience being accumulated within a reasonable time period for the results of research to be fed back to those dealing with newly occurring cases. Moreover computers can now deal so much more efficiently with data that series of a size that would be unmanageable by manual analysis can be coped with; also these large numbers make it possible for statisticians to do much more sophisticated calculations, and to use emerging methods for dealing with complex sets of data (Titterington, Murray, Parker, Spiegelhalter, Skene, Habbema and Gelpke, 1980). These have already made it possible to make confident predictions about the ultimate outcome of many severely head injured patients within a few days of injury (Jennett *et al.*, 1979). In place of the disappointingly vague optimism of this book there seems likely soon to be much more reliable data—as a basis not only

FORTHCOMING EVENTS

The 12th World Congress of Neurology will take place from September 20 to 25, 1981 in Kyoto International Conference Hall, Takaraike, Sakyo-ku, Kyoto 606, Japan.

Main themes are: (1) hemispheric specialization in man; (2) cerebral vascular disease; (3) neurotransmitter and neuropeptide dysfunction in relation to neurological disease; and (4) viral infections of the nervous system.

Further information can be obtained from:

Secretariat
12th World Congress of Neurology
c/o Simul International, Inc.,
Kowa Bldg No. 9
1-8-10, Akasaka, Minato-ku
Tokyo 107, Japan.

The Epilepsy International Congress 1981 will also be held in Kyoto, Japan during September 17–21, organized by Epilepsy International.

For further details apply to:

Dr Haruo Akimoto
Congress President
Epilepsy International Congress 1981
National Musashi Institute for Nervous and Mental Diseases
2620 Ogawa Higashi, Kodaira
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Selective Vulnerability of Neural Cells to Viral Infections. Richard T. Johnson 447

Familial Oculoleptomeningeal Amyloidosis. Hershel Goren, Marta C. Steinberg and Gholam H. Farboody ... 473

Dystrophia Myotonica and Myotonia Congenita Concurring in one Family: a Clinical and Genetic Study. C. J. Höweler, H. F. M. Busch, L. F. Bernini, E. van Loghem, P. Meera Khan and L. E. Nijenhuis ... 497

Nature of the Reversible White Matter Lesion in Multiple Sclerosis: Effects of Acute Inflammation on Myelinated Tissue studied in the Rabbit Eye. M. Dalakas, R. G. Wright and J. W. Prineas ... 515

The Duality of the Cingulate Gyrus in Monkey: Neuroanatomical Study and Functional Hypothesis. Christine Baleydier and François Mauguiere ... 525

Ammonia: Assessment of its Action on Postsynaptic Inhibition as a Cause of Convulsions. J. F. Iles and J. J. B. Jack ... 555

Clinical, Pathological, HLA Antigen and Immunological Evidence for Disease Heterogeneity in Myasthenia Gravis. D. A. S. Compston, A. Vincent, J. Newsom-Davis and J. R. Batchelor ... 579

Gliomatous Transformation and Demyelinating Diseases. Milne Anderson, Brodie Hughes, Michael Jefferson, W. Thomas Smith and J. A. H. Waterhouse ... 603

A New Method for the Microdissection of the Human Hypothalamus, with Mapping of Cholinergic, GABA and Catecholamine Systems in Twelve Nuclei and Areas. Hélène Langevin and Leslie L. Iversen ... 623

The Neurology of Visual Acuity. L. Frisén ... 639

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Hereditary Leucodystrophy in the Mouse: the new Mutant Twitcher. L. W. Duchen, Eva M. Eicher, Jean M. Jacobs, F. Scaravilli and Fernanda Teixeira ... 695

Notices of Recent Publications ... 711

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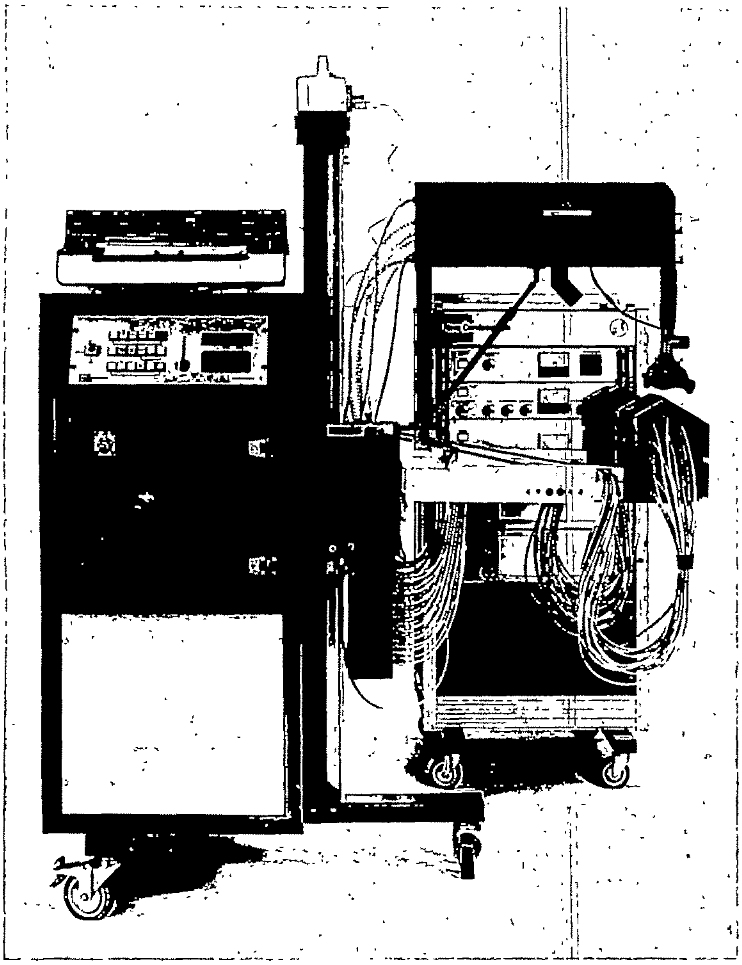

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SELECTIVE VULNERABILITY OF NEURAL CELLS TO VIRAL INFECTIONS

by RICHARD T. JOHNSON

(*From the Departments of Neurology and Microbiology,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland, U.S.A.*)

INTRODUCTION

THE nature of viruses and their ability to selectively affect specific neural cell populations was only dimly perceived one hundred years ago. In the inaugural volume of *Brain* a report on rabies does refer to the cause as a 'virus', although the term was used in its original, literal sense as a poison with comparisons to 'columbine and viperine' viruses (Fayrer, 1878). In the same volume a digest of a book on infantile paralysis clearly describes the selective vulnerability of the spinal anterior horn cells; however, the author failed to appreciate the infectious nature of the illness and ascribed poliomyelitis to 'a chill when the body was heated' (Crichton-Browne, 1878).

The present concept of viruses, the methods to recover and propagate viruses in the laboratory, and the definition of their physical-chemical properties have all evolved during this century. Even more recent advances in cellular and molecular biology have begun to define the many factors involved in selective cellular vulnerability. In the past two decades viruses, agents traditionally associated in neurology with acute inflammatory diseases of the nervous system, also have been implicated in malformations, tumours and degenerative, demyelinating and vascular diseases of the brain (Johnson and Narayan, 1974). Yet this seemingly extraordinary diversity of pathological lesions is explicable, in large part, by two simple principles underlying selective vulnerability: (1) varied cell populations of the CNS have different susceptibility to different viruses, and (2) viruses can have varied effects on different cells.

Both susceptibility to infection and varied disease processes are determined by the infectious cycle of the virus within individual host cells (fig. 1). Viruses, having no inherent mobility, are moved passively in extracellular spaces and encounter cell membranes at random. However, they do not infect cells randomly. To be susceptible to viral infection the host cell must have specific receptor sites accessible

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[1] Based on a talk given on April 5, 1978 at the Centenary of *Brain*.

on its cytoplasmic membrane. Given the intense specialization of the cytoplasmic membranes of neural cells, great variation in their susceptibility to different viruses would be anticipated. The presence or absence of viral receptors on the surface of CNS cells is only the first of a series of restrictions which determine specific vulnerability. To be susceptible to any form of infection a cell must also be capable of initiating penetration of the virus or its nucleocapsid (mainly through the process of endocytosis), and of releasing the nucleic acid from its nucleoprotein protective coat (uncoating). To produce progeny virus the cell must have the metabolic capacity to transcribe and translate virus-coded proteins, to replicate the viral nucleic acid, and, under direction of the viral genome, to assemble the virions. Any of these steps may not occur because of the specialized metabolic nature of the specific host cell. Extracellular infectious virus is released either by disruption of the cell, or, as with most enveloped viruses, by budding of the nucleocapsid through modified cell membranes during the final stages of assembly. Susceptibility is determined by the processes of adsorption, penetration and uncoating. The infection may be non-permissive, if complete viral protein and nucleic acid synthesis and virus assembly fail to occur, or permissive, if infectious virions are assembled. The extracellular spread of infection is dependent on virus release but this may be restricted within certain cells or by certain viruses.

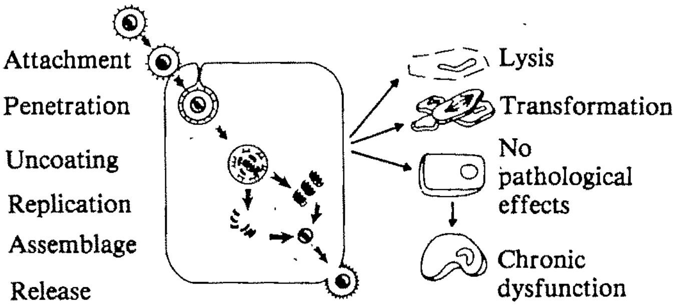


FIG. 1. Schematic diagram of the infectious cycle and its varied effects on the host cell. The nucleus and cytoplasm are not shown, since different viruses are replicated and assembled in different locations. The schema portrays an enveloped virus, but some enveloped viruses lose their envelope by fusion in the process of penetration; the envelopes of progeny virions may be acquired from modified nuclear, cytoplasmic or plasma membranes. For simplification the transcription of messenger RNA and translation of non-structural proteins have not been included. The effects on host cells (*right*) do not necessarily require a complete infectious cycle. (Reprinted from Johnson (1974).)

The infectious cycle of a given virus or a portion thereof may have varied effects on the host cell (Robb, 1977). Adsorption alone can alter the cytoplasmic membrane leading to fusion with adjacent cell membranes or even cell lysis. During virus synthesis the production of cellular proteins and nucleic acids may be inhibited to greater or lesser extent. Furthermore, virus-specific proteins may alter cell function, and infection can increase the permeability of lysosome membranes. The classic effect of viral infection is cell lysis represented in tissues by cell necrosis.

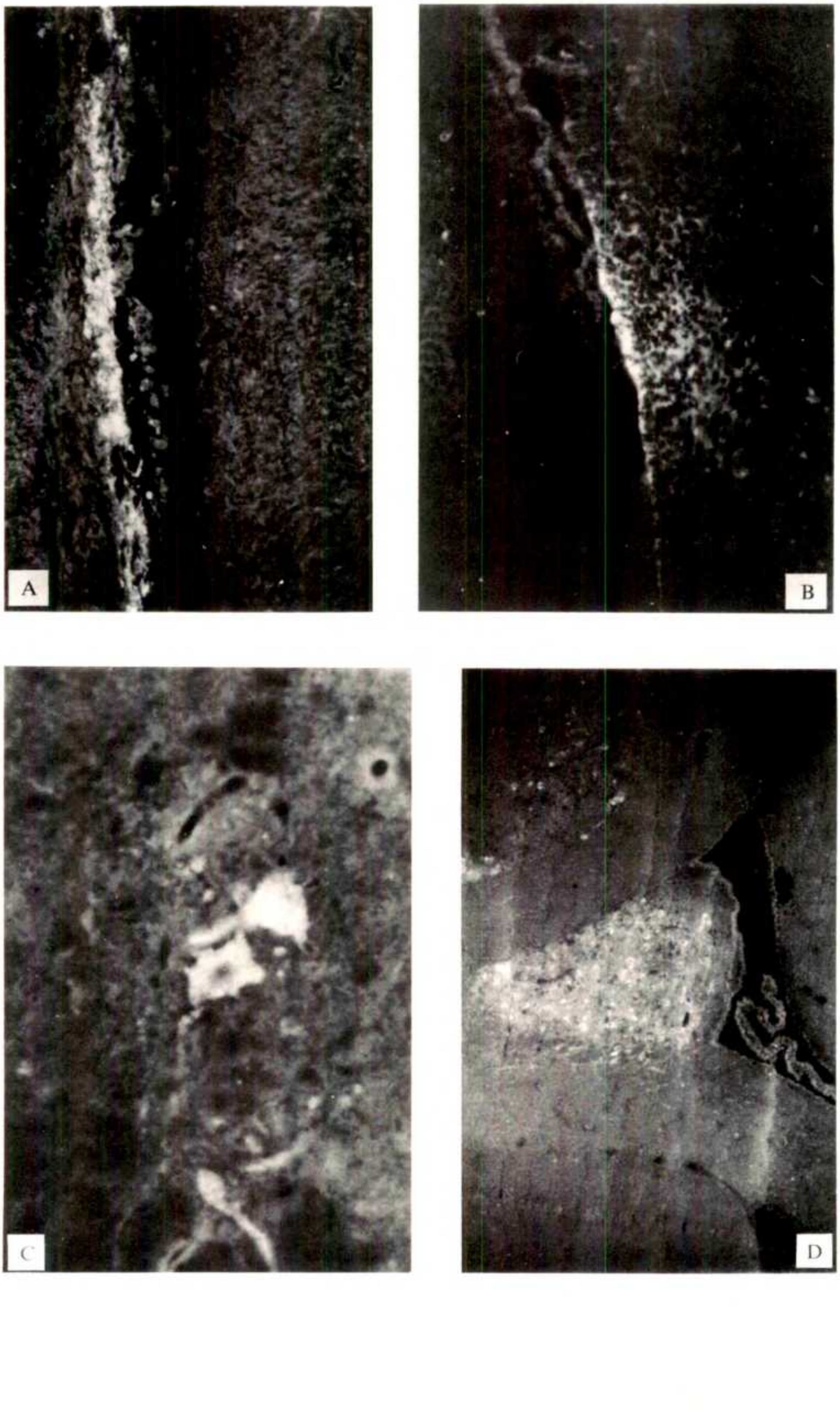
Alternatively, infection may result in cell transformation represented *in vitro* by the piling up of cells in culture and the establishment of 'immortal' cell lines and represented *in vivo* by tumour formation. Transformation does not necessarily involve permissive infection or the production of morphologically identifiable viral structures. In such instances the sequestered viral genome codes for proteins that presumably disrupt contact inhibition and allow unregulated cell division. Finally, the infectious process may have no obvious effect on the morphological integrity of the cell, yet this non-cytopathic infection may alter specific cell functions, inhibit mitotic activity, or even cause premature senescence.

ACUTE INFECTIONS

In acute infections of experimental animals virus replication in the CNS may be limited to meningeal cells or meningeal and ependymal cells (fig. 2A). Presumably this represents the experimental counterpart of human viral meningitis, most commonly seen with enterovirus and mumps virus infections, where symptoms and signs are limited to headache, fever, stiff neck and pleocytosis. Other viruses or the same viruses in experimental hosts of different ages or species may spread to neural parenchymal cells (fig. 2B) causing encephalitis with obtundation, convulsions, paralysis and death. This simulates encephalitis in man complicating infections with several togaviruses and herpesviruses. Both the virus and host susceptibility determine the invasiveness and neurovirulence of the infection (Johnson and Mims, 1968).

Some viruses selectively involve only specific neural cell populations, and these infections may be associated with characteristic clinical syndromes. Classic examples in man and animals are poliomyelitis virus infections, in which selective vulnerability of anterior horn cells leads to a characteristic lower motor neuron paralysis (fig. 2C). (Jubelt, Gallez-Hawkins, Narayan and Johnson, 1980) and rabies, in which the early infection involves neurons of the limbic system (fig. 2D) (Johnson, 1965). Because of the lack of early involvement of cortical neurons in rabies, obtundation, seizures and motor deficits are initially absent. Instead, the rabid animal may be alert, lose timidity, and show aberrent sexual and aggressive behaviour. This appears to be a diabolical adaptation of rabies viruses to animals in which selective infection of limbic neuronal populations modifies behaviour, thus driving the host in a fury to transmit the virus to another host (Johnson, 1971).

Selective vulnerability of specific cell types or populations may not be the sole explanation of characteristic clinical signs and symptoms. For example, herpes simplex virus encephalitis in adults tends to localize to the orbital-frontal and medial-temporal regions of brain resulting in the prominence of behavioural abnormalities, hallucinations and aphasia. However, this localization does not appear to result from the selective vulnerability of a specific cell population, since herpesvirus antigens and inclusions are found in both neurons and glia over a contiguous area including functionally diverse entorhinal and neocortical structures.


A
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D

Several years ago it was postulated that this localization might result from virus entry into the CNS by way of the olfactory fibres with subsequent spread along the base of the brain within the anterior and middle fossæ (Johnson and Mims, 1968). However, failures to consistently find evidence of infection of olfactory bulbs, the observation that patients with recurrent herpes labialis may develop herpetic encephalitis (Leider, Magoffin, Lennette and Leonards, 1965) and the demonstration that type 1 herpes simplex virus is latent in the trigeminal ganglia in the majority of adults (Baringer, 1975) suggest that activation of virus in the ganglia rather than primary infection may lead to herpetic encephalitis. Fibres from a portion of the trigeminal ganglia extend to the meninges of the base of the anterior and middle fossæ. In an occasional patient activation may disseminate virus in the distribution of these fibres rather than, as commonly occurs, in the distribution of fibres to the lips or oropharynx. Resulting cerebral infection would remain localized not because of selective vulnerability of specific cells but because antibody would limit virus spread to contiguous cells (Davis and Johnson, 1979).

MALFORMATIONS

In general, undifferentiated cells are more susceptible to viral infection than differentiated cells. During ontogeny of the CNS the generation, migration, and differentiation of cells at different times presents a kaleidoscope of cell vulnerability, and infections at different times during development can lead to varied sequelæ. In the human fœtus rubella and cytomegalovirus infections can lead to persistent, inflammatory infections of the CNS (Johnson, 1978). However, in natural and experimental CNS infections of fœtal and neonatal animals, virus infections have been shown to lead to malformations which lack inflammation, gliosis, calcification, or inclusion bodies to suggest antecedent or persistent infection. Indeed, these malformations resemble human malformations presumed to have a toxic, genetic or vascular basis. Furthermore, the viruses associated with these malformations are not a select group of 'teratogenic' viruses, but are representative of a wide range of virus families (Table 1).

FIG. 2. Selective vulnerability of neural cells in acute viral infections. Fluorescent antibody staining shows sites of virus replication in rodent brains after intracerebral inoculation of viruses. A, vaccinia virus infection is limited to meningeal cells. Newborn hamster brain is shown two days after inoculation. × 200. B, sindbis virus (an arbovirus) infects meningeal, ependymal, and parenchymal cells. Adult mouse brain is shown with antigen in ependymal cells and underlying glial cells four days after inoculation. × 60. C, poliovirus type 2 (Lansing strain) selectively infects neurons. Adult mouse cervical spinal cord is shown with antigen only in limited numbers of anterior horn cells six days after inoculation. × 300. (Reprinted from Johnson, Brooks, Jubelt and Swarz, 1979.) D, rabies virus selectively infects neurons of the limbic system. Adult mouse brain six days after inoculation of the CVS strain shows prominent involvement of neurons of the septal nucleus. Antigen is also present in some neurons of the indusium griseum (supracallosal hippocampus) (*above left*) but not in putamen (*right*) or thalamus (*below*). × 60. (Reprinted from Johnson, 1965.)

TABLE I. EXPERIMENTAL CEREBRAL MALFORMATIONS INDUCED BY VIRUSES

Malformation	*Virus*	*Host species*
Defects in neural tube	Myxoviruses	
	Influenza	Chick embryo
	Newcastle disease	Chick embryo
Encephalocele	Togavirus	
	St. Louis encephalitis	Mouse
Cerebellar hypoplasia	Parvoviruses	
	Rat virus	Hamster, rat, cat, ferret
	Feline panleukopenia	Cat, ferret
	Minute virus of mice	Mouse
	Arenaviruses	
	Lymphocytic choriomeningitis	Rat
	Tamiami	Mouse
	Unclassified	
	Bovine viral diarrhœa	Cow, sheep
	Hog cholera	Pig
Hypomyelinization	Unclassified	
	Hog cholera	Pig
	Border disease	Sheep
Hydranencephaly	Orbivirus	
	Bluetongue	Sheep
	Togavirus	
	Akabane	Cow, sheep
Porencephaly	Orbivirus	
	Bluetongue	Sheep, mouse, Hamster
	Togaviruses	
	Venezuelan equine encephalitis	Monkey
	Akabane	Sheep
Hydrocephalus	Myxoviruses	
	Mumps	Hamster, monkey
	Parainfluenza, type 1, 2	Hamster, mouse
	Influenza	Hamster, mouse, monkey
	Measles (mutant)	Hamster
	Newcastle disease	Mouse
	Reoviruses	
	Type 1	Mouse, hamster, rat, ferret
	Type 3 (mutant)	Mouse
	Togaviruses	
	Japanese encephalitis	Pig
	Ross River	Mouse
	St. Louis encephalitis	Mouse

Modified from Johnson, 1978.

The pathogenesis of anomalies is varied. Three examples, which we have studied, will be summarized to illustrate different mechanisms. Neonatal viral infections of ependymal cells demonstrate how many different viruses can produce a similar malformation; studies of bluetongue virus in sheep show that the same virus may produce different malformations with infection at different stages of gestation; and parvovirus-induced cerebellar hypoplasia exemplifies how mitotic activity can determine selective vulnerability.

Virus-induced aqueductal stenosis with hydrocephalus was first recognized after mumps virus infections of newborn hamsters (Johnson, Johnson and Edmonds, 1967). During a study of a neuro-adapted strain of mumps which infected neurons, non-adapted hamster strains were inoculated to serve as controls. Although the animals inoculated with non-adapted virus showed no evidence of clinical disease, virus growth occurred and viral antigen was found almost exclusively in ependymal cells (Johnson, 1968). However, within two weeks virus was cleared, viral antigen was no longer detectable, and the accompanying inflammatory response had resolved. Despite normal growth and development during the ependymal cell infection, two to six weeks after acute infection had resolved, these animals developed hydrocephalus involving the lateral and third ventricles (fig. 3A). Stenosis or occlusion of the aqueduct of Sylvius was consistently found, and remaining ependymal cells in the area of the stenosis formed rosettes or aqueductules. Furthermore, the area normally occupied by the aqueduct was not replaced by glial tissue but contained normal brain-stem parenchyma, and normal tissue appeared to extend between clusters of residual ependymal cells (Johnson and Johnson, 1968). Thus, by the time that clinical disease evolved, the stenotic aqueduct fulfilled all the histological criteria proposed in human neuropathology to establish a diagnosis of primary agenesis of the aqueduct (Russell, 1949).

Virus-induced hydrocephalus also can develop in laboratory animals when spinal fluid pathways are obstructed by inflammatory cells or by neoplastic transformation of the meningeal cells or when cell loss due to chronic infection of the brain leads to hydrocephalus *ex vacuo*. However, an acute ependymal infection with a delayed development of aqueductal stenosis appears to be a common mechanism, and identical lesions can be induced with a variety of viruses in several species of animals (Johnson and Johnson, 1969; Johnson, 1975). A similar pathogenesis of aqueductal stenosis may also occur in man. Subsequent to the experimental studies, a number of reports described children who developed hydrocephalus months after mumps virus infections (reviewed in Johnson, 1975). Furthermore, our ultrastructural studies of human cerebrospinal fluid sediment from patients with mumps meningitis showed ependymal cells, and these cells contained cytoplasmic tubules consistent with mumps virus nucleocapsids (Herndon, Johnson, Davis and Descalzi, 1974). The case reports and the demonstration of selective vulnerability of human ependymal cells to mumps virus provide circumstantial evidence that mumps virus may cause acquired hydrocephalus in children. As yet, no virus has been conclusively related to congenital hydrocephalus in man, although a

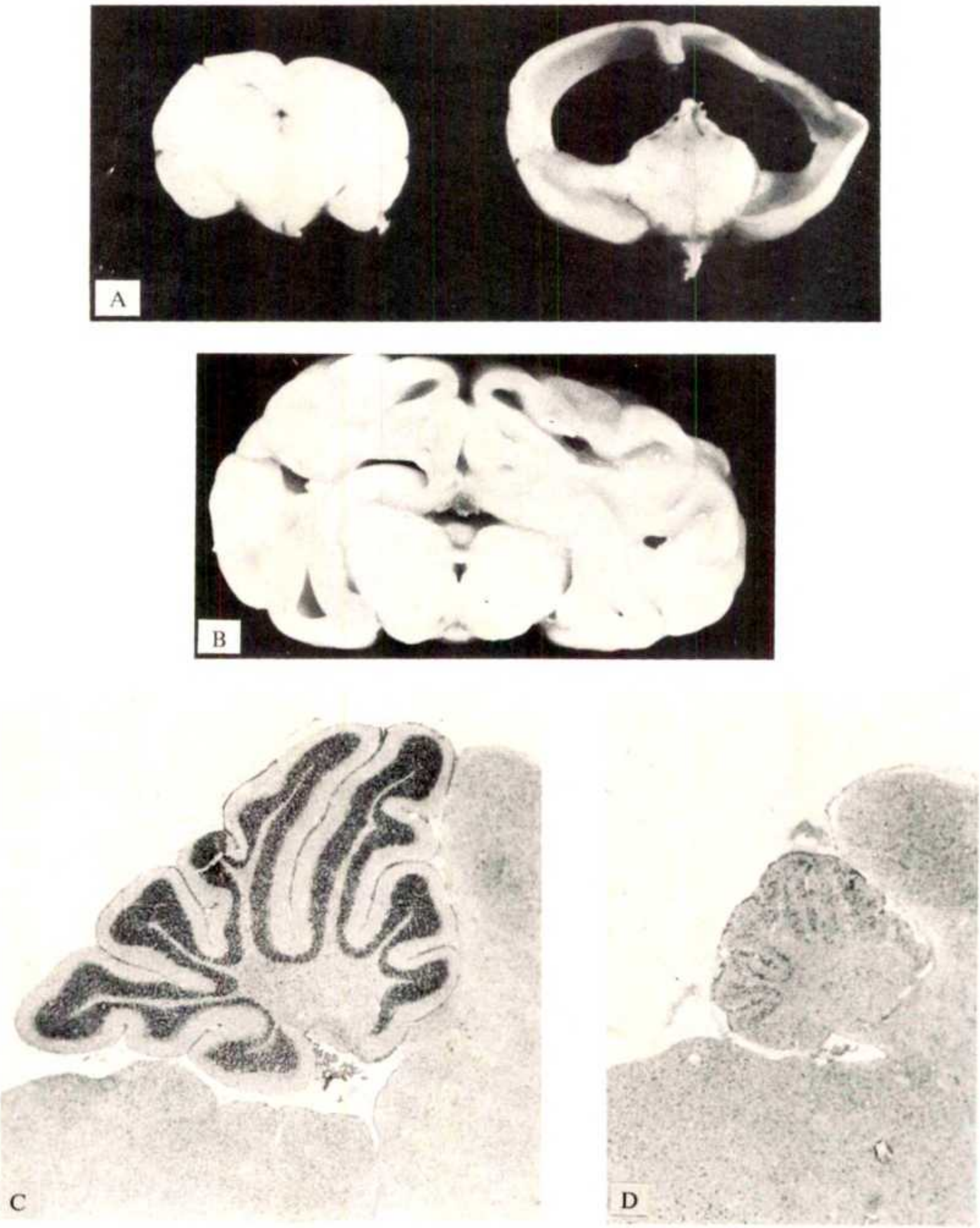

FIG. 3. Experimental malformations resulting from fœtal or neonatal infections. A, hydrocephalus (*right*) is shown in a 4-week-old hamster after neonatal infection with mumps virus; normal brain (*left*) is from hamster that received virus plus antiserum. × 3. (Reprinted from Johnson *et al.*, 1967.) B, porencephalic cysts are shown in the brain of 120-day fœtal lamb inoculated intramuscularly with bluetongue vaccine virus at mid-gestation (77 days). (Reprinted from Osburn, Silverstein, Prendergast, Johnson and Parshall, 1971.) C and D, granuloprival cerebellar degeneration (D) is shown in a 21-day-old hamster after neonatal infection with rat virus. Normal littermate is shown in C. × 33.

serological study has implicated lymphocytic choriomeningitis virus (Sheinbergas, 1975).

Bluetongue virus is a double-stranded RNA virus which causes respiratory and gastrointestinal disease in sheep and cattle. In adult sheep the disease is characterized by fever, ulcerations of the oral mucosa, focal necrosis of cardiac muscle, and pulmonary œdema. The mortality rate ranges from 2 to 30 per cent, but no lesions are recognized in the CNS (Howell and Verwoerd, 1971). In the 1950s an attenuated live virus-vaccine was developed in chick embryos, and widespread immunization of sheep was initiated. The live virus-vaccine caused no clinical disease and conferred good immunity. However, in the subsequent lambing season large numbers of abnormal lambs were delivered by ewes vaccinated during pregnancy. In these lambs lesions were confined to the CNS (Young and Cordy, 1964). Although maternal inoculation caused a variable frequency of anomalies, direct intramuscular inoculation of the fœtal lambs was found to consistently cause malformations. Lambs inoculated at fifty days of gestation (end of first trimester) were born with hydranencephaly, lambs inoculated at seventy-five days of gestation (mid-term) had porencephalic cysts (fig. 3B), and lambs infected after one hundred days of gestation showed no gross abnormalities but only microscopic glial nodules in the brain (Osburn, Silverstein, Prendergast, Johnson and Parshall, 1971). Sequential virological and pathological studies demonstrated that the vaccine-virus selectively infected the germinal cells of the subventricular zone (Osburn, Johnson, Silverstein, Prendergast, Jochim and Levy, 1971). This was accompanied by an acute necrotizing encephalitis in the subventricular zone, which in early gestation caused destruction of most germinal cells and led to hydranencephaly. By mid-gestation the neuronal layers of the ovine cortical mantle are largely formed, and the subventricular zone consists primarily of glial cell precursors. Destruction of these cells led to focal areas of necrosis with subsequent production of porencephalic cysts. In either situation by the time of birth, virus had been cleared, virus antigen was no longer detectable, the inflammatory response had resolved, and macrophages had cleared necrotic cell debris leaving a glial walled cavity bearing no features to suggest the antecedent encephalitis. Thus, two different malformations were caused by the same virus, and the type of malformation was dependent on which cells were being generated and were migrating at the time of the infection.

Viral destruction of a different population of immature cells was found in 1964 when Kilham and Margolis reported granuloprival cerebellar degeneration after intracerebral inoculation of neonatal hamsters with rat virus, a single-stranded DNA virus. Their sequential histological studies showed selective destruction of the external germinal cells of the cerebellum prior to their post-natal migration to form the granular cell layer. This led to a small cerebellum with abnormalities of foliation (fig. 3D), total or subtotal absence of granular cells, and aberrent synaptic organization (Herndon, Margolis and Kilham, 1971). Rat virus produced similar lesions in neonatal rats, cats and ferrets. Furthermore, feline panleukopenia virus, another parvovirus, was shown to be the cause of spontaneous ataxia in kittens

(Kilham and Margolis, 1966), a common neurological disorder of domestic cats previously thought to be a genetic abnormality.

Thus, bluetongue virus causes abnormalities of the forebrain and parvoviruses hypoplasia of the cerebellum. This difference is explained, in part, by the failure of bluetongue virus to infect the germinal cells of the cerebellum. However, rat virus does infect the germinal cells of the subventricular zone as well as the cerebellum even though no subsequent malformation of the forebrain is evident (Lipton and Johnson, 1972). To compare these infections we adapted the bluetongue vaccine virus to rodents (Narayan and Johnson, 1972) and carried out parallel studies of bluetongue and rat virus infections in subventricular zones of neonatal hamsters. Both viruses infected the same cells and comparable amounts of infectious virus were replicated. However, bluetongue virus infections spread outward from the subventricular zone to the cortex, dentate nucleus, hippocampus and internal granular cells of the olfactory bulb. In contrast, rat virus infection remained confined to the subventricular zone (Becker, Narayan and Johnson, 1974).

Although the same cell population was susceptible, the mechanisms of susceptibility clearly differed. Rat virus, a single-stranded DNA virus, is capable of replication only in cells synthesizing cellular DNA. Therefore, only actively dividing cells in the subventricular zone were susceptible, and post-mitotic neuroblasts and glial cells could no longer replicate virus. Over the brief interval of the acute infection some germinal cells of the forebrain were destroyed presumably leading to a minor depletion of cell numbers within specific neuronal layers or glial populations. In contrast, bluetongue virus does not require cellular DNA synthesis for replication and susceptibility appears dependent on a lack of cellular differentiation. Thus, although both viruses initially infect subventricular germinal cells, the basis of their susceptibility differs. Considering the biological properties of these cells and of these viruses it is reasonable that bluetongue virus infections spread outward along migratory pathways of undifferentiated cells involving major portions of the forebrain, whereas rat virus is biologically restricted to the specific zone of mitotic activity.

CEREBRAL NEOPLASMS

Mitotic activity is also an important factor in the selective vulnerability of cells to viral transformation. As in malformations, this aids in explaining the vulnerability of the developing nervous system to virus-induced tumours, and the dependence on mitotic activity also explains the localization and histological types of virus-induced cerebral neoplasms. Unlike chemical carcinogens, the ability of viruses to cause neoplasia depends on alteration of host cell DNA, usually by the incorporation of all or part of the viral genome into the host cell DNA. Cells in culture generally need to be dividing in order to be transformed, and DNA synthesis associated with mitosis or possibly with DNA repair are presumably prerequisites to viral transformation *in vivo*.

TABLE 2. EXPERIMENTAL CEREBRAL NEOPLASMS INDUCED BY VIRUSES

Tumour type	*Virus*	*Host*
Sarcomas	Polyoma	Hamster, rat
	Bovine papilloma	Hamster
	Adenovirus, type 12	Hamster
	Adenovirus, type 18	Hamster
	Simian adenovirus	Hamster
	Avian sarcoma	Chicken, turkey, rabbit, dog, rat, monkey
	Murine sarcoma	Rat, mouse
Meningioma	JC	Hamster
	Bovine papilloma	Hamster, calf
	Murine sarcoma	Rat
Ependymoma and choroid plexus papillomas	SV40	Marmoset, hamster
	BK	Hamster
	JC	Hamster
	Avian adenovirus (CELO)	Hamster
	Avian sarcoma	Dog
Hæmangioma	Polyoma	Rat
	Murine sarcoma	Rat
Medulloblastoma	JC	Hamster
	Adenovirus, type 12	Mouse
	Simian adenovirus	Hamster
	Avian sarcoma	Dog
Gliomas	JC	Monkey
	Avian sarcoma	Hamster, mouse, rat, guinea-pig, dog, cat, marmoset
	Murine sarcoma	Rat
	Simian sarcoma	Marmoset
Neuroblastoma	Adenovirus, type 12	Rat

Although no virus has been clearly associated with a naturally occurring brain tumour in animals or man (Bigner and Pegram, 1976), a wide variety of cerebral neoplasms have been experimentally produced by viruses (Table 2). The oncogenic viruses include DNA viruses of the papovavirus (polyoma, bovine papilloma, SV40, BK, JC) and adenovirus (human and simian) families and RNA viruses of the retrovirus family (avian sarcoma, murine sarcoma, and simian sarcoma viruses) (Bigner and Pegram, 1976; Ikuta and Kumanishi, 1973). The oncogenic RNA viruses contain an RNA-dependent DNA polymerase (reverse transcriptase) which allows production of a DNA provirus synthesized from viral RNA. Double-stranded DNA is then made which can be integrated into host cell DNA.

In general, DNA viruses produce neoplasms only in unnatural hosts, and development of cerebral neoplasms usually requires intracerebral inoculation of neonatal animals. Since the cells transformed by these viruses are not permissively infected (that is, progeny virus is not produced), there is a lack of amplification or dissemination of virus. Therefore, the dose of virus delivered and the site of inoculation determine, in part, the frequency or cell type of the neoplasm. Adenoviruses are generally not recoverable from tumours, but the tumour cells produce adenovirus-coded proteins and molecular hybridization has demonstrated the presence of viral DNA in the tumour cells; therefore, only a segment of the viral genome is probably integrated. Papovavirus-induced tumours contain little, if any, infectious virus and no morphological evidence of virions, but fusion of tumour cells to permissive cells usually yields infectious virus indicating the presence of the entire genome.

The RNA sarcoma viruses produce tumours both in their natural host as well as a wider range of other hosts, and the transformed cells are often permissively infected and produce infectious virions. However, the degree of susceptibility and permissiveness are host-dependent. For example, Rous sarcoma virus, a chicken virus, induces tumours more readily in chickens than mammals, and transformed chicken cells produce more virus that transformed mammalian cells (Ikuta and Kumanishi, 1973). Further, the production of virus by RNA virus transformed cells allows dissemination and accounts for the potential to cause cerebral tumours after extraneural inoculation.

Many virus-induced tumours are undifferentiated, but among those which can be classified the predominance of sarcomas, ependymomas, hæmangiomas and medulloblastomas is not surprising, since these tumours arise from CNS cells which show mitotic activity in the neonatal animal. The reproducibility of these tumours as 'models' is variable because multiple tumour types are often produced by a single virus. However, some strains of Rous sarcoma virus in rats yield a predominance of gliomas (Wilfong, Bigner, Self and Wechsler, 1973); SV40 and BK virus in hamsters cause only ependymomas and choroid plexus papillomas (Greenlee, Narayan, Johnson and Herndon, 1977), and some strains of JC virus in the hamster yield a preponderance of medulloblastomas (Padgett, Walker, ZuRhein and Varakis, 1977).

The type of tumour is also determined to some extent by the site of inoculation. In dogs Rous sarcoma virus inoculation deep into the cerebral hemispheres leads to gliomas, which appear to arise from the subependymal germinal cells; whereas subarachnoid inoculation leads to sarcomas, which develop from meningeal cells (Bigner, Kvedar, Shaffer, Vick, Engel and Day, 1972). Although it has been possible to produce glial cell tumours in adult animals with some of the RNA sarcoma viruses, even in these instances the target cells appear to be those glial precursor cells continuing to replicate in the subventricular zone (Ikuta and Kumanishi, 1973). Therefore, the selective vulnerability of neural cells to transformation depends on the transforming ability of the virus, the delivery of high titred inoculum in the area of the target cell, and the state of the DNA in the potential host cell.

DEGENERATIVE DISEASES

The association of transmissible agents with progressive non-inflammatory neuronal loss has been established in animals and in man (Table 3). These spongiform encephalopathies are regarded by some as the classical slow infections (Gajdusek, 1977; Oldstone, Lampert, Lee and Dixon, 1977). The majority are due to the poorly defined subacute spongiform encephalopathy agents, but a similar encephalomyelopathy has recently been associated with a murine retrovirus.

TABLE 3. DEGENERATIVE DISEASES CAUSED BY VIRUSES (SPONGIFORM ENCEPHALOPATHIES)

Virus	*Natural host*	*Experimental hosts*
Unconventional agents		
Scrapie	Sheep, goat	Mouse, rat, guinea-pig, mink, hamster, ferret, some old and new world monkeys
Transmissible mink encephalopathy	Mink	Sheep, goat, hamster, ferret, some old and new world monkeys
Kuru	Man	Chimpanzee, old and new world monkeys, mink, ferret
Creutzfeldt-Jakob disease	Man	Chimpanzee, old and new world monkeys, cat, mouse, guinea-pig, hamster, ferret
Conventional viruses		
Murine neurotropic retrovirus	Wild mouse	'N-tropic' mouse

Scrapie, a natural disease of sheep and goats, has been recognized for over two hundred years and was long regarded as a genetically transmitted, cerebellar degenerative disease. Although initially transmitted experimentally in the 1930s, thirty years of debate ensued regarding its genetic or infectious transmission. Transmissible mink encephalopathy was first observed in the 1950s and probably originated from the feeding of scrapie-infected meat to mink, with subsequent spread from mink to mink (Burger and Hartsough, 1965). Kuru is an endemic degenerative disease of the Fore linguistic group in the Eastern Highlands of New Guinea first described by Gajdusek and Zigas in 1957. Because of similarities to scrapie in its tribal localization, its ingravescent afebrile course with cerebellar signs, and its histopathological features of neuronal loss with vacuolization and gliosis (Hadlow, 1959), analogous transmission to subhuman primates was initiated in

1960. The initial successful transmission to chimpanzees occurred after incubation periods of one to six years (Gajdusek, 1977). Creutzfeldt-Jakob disease is epidemiologically and clinically distinct from the other spongiform encephalopathies. Its distribution is worldwide and, although most cases are sporadic, about 10 per cent are familial with an autosomal dominant genetic pattern (Masters, Harris, Gajdusek, Gibbs, Bernoulli and Asher, 1978). The spongiform degeneration in Creutzfeldt-Jakob disease resembles that in scrapie and kuru but is most striking in the cerebral cortex explaining the clinical presentation of rapidly progressive dementia with myoclonus and the variable presence of other motor and sensory findings (Roos, Gajdusek and Gibbs, 1973).

Although each of these diseases is experimentally transmissible to a variety of other host animals (Table 3), the exact mode of transmission in nature is not clear (Gajdusek, 1978). The transmission of scrapie appears to require early life contact between animals. Kuru and transmissible mink encephalopathy both appear to have been transmitted by cannibalism. Creutzfeldt-Jakob disease is the most mysterious, particularly since the familial cases are transmissible in the laboratory. The relative paucity of conjugal cases, the lack of geographical or temporal clustering of cases, and the distribution among all occupational groups indicate a relative lack of infectivity, although the disease is clearly transmissible in man as shown by the unfortunate medical transmission in the course of corneal transplantation and stereotactic recordings (Duffy, Wolf, Collins, De Voe, Streeten and Cowen, 1974; Bernoulli, Siegfried, Baumgartner, Regli, Rabinowicz, Gajdusek and Gibbs, 1977).

The reason for the selective vulnerability of neurons and relative selective neuronal populations in different spongiform encephalopathies are not known. Infectivity is found in many of the tissues, but only rarely in blood or cerebrospinal fluid and not in urine, stool or respiratory secretions (Gajdusek, 1978). This distribution may account for the relative lack of natural infectivity. Following extraneural inoculation of scrapie, infectivity first develops in lymphoid tissues and after several months can be found in the brain. Viral titres increase slowly in brain until pathological and clinical findings evolve (Eklund, Kennedy and Hadlow, 1967). There is disagreement as to whether early neuronal vacuolization or astrocytic proliferation is the first and primary event. Astrocytic proliferation analogous to transformation with secondary neuronal loss has been postulated (Eklund, *et al.*, 1967); however, most investigators believe that the neuronal vacuolization and loss is primary with a secondary astrocytosis (Masters and Richardson, 1978). Both might be partially true. Evidence from cell separation studies indicates greater infectivity in neurons than in glial cells (Narang, Shenton, Giorgi and Field, 1972); but since the unconventional spongiform encephalopathy agents have not been visualized with the electron microscope, fail to produce cytopathic changes in cell cultures, and evoke no immune responses which might allow immunocytochemical localization, pathogenetic studies at a cellular level have not been feasible.

It has been postulated that infection with spongiform encephalopathy agents causes chronic disorders of host cell function, eventually leading to metabolic abnormalities and premature cell death. Based on such a hypothesis, if all cells in the body were infected, the high metabolic rate and low regenerative capacity of neurons might cause them to be the first cells to show pathological and functional abnormalities (Johnson, 1967).

Other explanations for spongiform degeneration have been suggested by our studies of a murine polioencephalomyelopathy caused by a conventional virus, a murine retrovirus. The natural infection of mice causes slowly progressive upper and lower motor neuron signs (Officer, Tecson, Estes, Fontanilla, Rongey and Gardner, 1973). After experimental infection of mice, infectivity first increases in the spleen with later involvement of the CNS and other organs. When virus concentration reaches a threshold level, clinical signs and pathological abnormalities limited to the CNS evolve (Brooks, Swarz, Narayan and Johnson, 1979). This sequence of virus spread and the non-inflammatory vacuolization and neuronal loss resemble scrapie in mice. Furthermore, the cytoplasmic vacuoles in neurons and glial cells contain fragments and swirls of membranes resembling those seen in the spongiform encephalopathies caused by unconventional agents (fig. 4A) (Lampert, Gajdusek and Gibbs, 1972). However, during the early phase of vacuolization and clinical disease the evidence of virus growth, as judged morphologically by the budding of virions from cytoplasmic membranes, is limited to vascular endothelial cells and pericytes (fig. 4B) (Swarz, Brooks and Johnson, 1978.) Possible explanations for this paradox of virus growth in structurally normal cells and pathological changes in apparently uninfected cells include: (1) neurons and glia may be non-permissively infected (that is, harbour the genome with some protein production but without assemblage of morphologically identifiable virus); (2) a viral protein may be released which is toxic to the neurons and glia; or (3) the vacuolization may be secondary to altered function of the infected vascular endothelial cells. At least in this system the pathogenesis of spongiform encephalopathy can be investigated with an agent which can be visualized, studied immunologically, and assayed in cell cultures.

DEMYELINATING DISEASES

Viral infections have been associated with acute and chronic demyelination in human disease and in natural and experimental diseases of animals (Table 4). However, the mechanisms of virus-induced demyelination are varied (Weiner, Herndon and Johnson, 1973).

The JHM strain of mouse hepatitis virus causes acute demyelination in mice by the selective infection of oligodendrocytes (Lampert, Sims and Kriazeff, 1973). Immunosuppression does not prevent this demyelination (Weiner, 1973). In addition to the acute lesions, virus persists in surviving mice and subclinical focal demyelination can occur for many months (Herndon, Griffin, McCormick and Weiner, 1975). In contrast, during acute Theiler's virus infection of mice there is

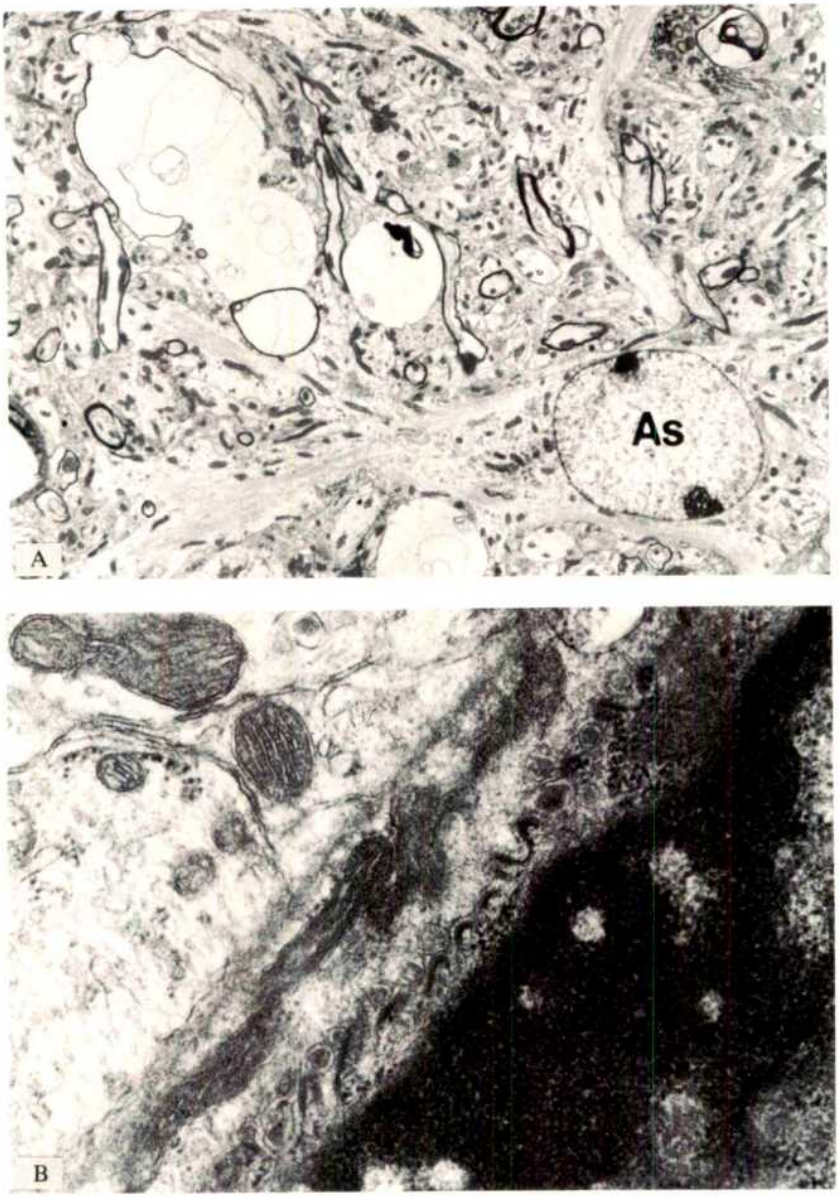

FIG. 4. Spongiform polioencephalomyelopathy caused by a murine neurotropic retrovirus. A, lumbar spinal cord of a mouse thirty days after intracerebral inoculation shows non-inflammatory vacuolization. Vacuoles contain curled membranes and absence of virions and resemble the vacuoles in scrapie. Reactive astrocyte (AS) shows numerous microfilaments. × 2900. B, lumbar spinal cord twenty-one days after inoculation shows C-type viruses budding from abluminal cytoplasmic membrane of otherwise intact pericyte (*lower right*). × 42,000. (Reprinted from Johnson *et al.*, 1979.)

TABLE 4. DEMYELINATING DISEASES CAUSED BY VIRUSES

	Animals	*Man*
Acute disease	Mouse hepatitis virus (mouse, rat)	Viruses associated with para-infectious encephalomyelitis and acute necrotizing hæmorrhagic leukoencephalitis
Subacute or chronic disease	Theiler's virus (mouse) Canine distemper virus (dog) Visna virus (sheep) Caprine leukoencephalitis virus (goat)	Measles in subacute sclerosing panencephalitis. Papovaviruses in progressive multifocal leukoencephalopathy

selective infection of neurons, and the later demyelinating disease appears to be immune-mediated (Lipton, 1975). That is, the pathological changes are not ultimately induced by products of the viral genome, but by a cellular or humoral immune response to those products. When anti-lymphocyte serum is given to mice with this infection, the initial neuronal infection and destruction is enhanced, but the later demyelination is prevented (Lipton and Dal Canto, 1976). This demyelination may result not from specific attack on virus proteins associated with the oligodendrocyte or myelin sheath but may involve a mechanism termed the 'innocent bystander' effect—a mechanism in which macrophages recruited into the area of neuronal infection may release proteases which non-specifically lead to the dissolution of the myelin sheaths (Cammer, Bloom, Norton and Gordon, 1978).

The mechanism for demyelination in subacute or chronic canine distemper virus infections is not known. Virus antigen seems most prominent in the perivascular cells with only patchy involvement of neurons and glia. Electron microscopic studies have demonstrated virus particles primarily in astrocytes rather than oligodendrocytes (McCullough, Krakowka and Koestner, 1974; Raine, 1976). It has been proposed on a theoretical basis that demyelination may be immune-mediated or that virus released from infected astrocytes causes fusion and disruption of myelin membranes (Choppin, 1968). The latter postulated mechanism could account for virus-induced demyelination without either infection of oligodendrocytes or the involvement of immune responses.

In retrovirus infections leading to visna in sheep and leukoencephalitis in goats even more complex mechanisms appear to lead to the chronic disease and demyelination. Visna, the prototype of slow infections due to conventional viruses, has a long incubation period and causes progressive paralytic disease with inflammatory lesions primarily in white matter (Sigurdsson and Pálsson, 1958). The long latency period of visna can be explained by the finding that this RNA virus persists in sheep CNS as a DNA provirus intermediate (Haase, Stowring, Narayan, Griffin and Price, 1977). Virus can be recovered by co-cultivation of brain or leukocytes at any time during the incubation period. The infected sheep develop a cellular and humoral immune response to the agent (Griffin, Narayan and Adams, 1978), but in the chronically infected animal new and fully virulent viruses can be recovered which are not neutralized by the antibody formed against the initial infecting agent (Narayan, Griffin and Clements, 1978). This antigen shift of visna virus in the sheep appears to result from multiple mutations in the virus genome (J. E. Clements, unpublished data), so that new viruses arise which can lead to exacerbations of disease. The cumulative effect of lesions induced by serial mutations may give rise to the apparent progressive neurological disease. Why the lesions are located primarily in the white matter, what role the striking inflammatory response may play in the demyelinating process, and whether oligodendrocytes do or do not contain the virus or are susceptible to virus infection are questions yet to be answered.

Post-infectious encephalomyelitis and acute hæmorrhagic necrotizing leukoencephalitis are acute human demyelinating diseases which have long been associated with a viral infection, but little is known of their pathogenesis. It is not even known whether there is an obligatory replication of virus in the brain or whether cell-mediated immune mechanisms similar to those in experimental allergic encephalitis are involved in the perivenular demyelination. In subacute sclerosing panencephalitis the variable degrees of demyelination appear to be related to oligodendrocyte infection as judged by the presence of measles virus antigen and inclusions in oligodendrocytes within demyelinated areas. Immunopathological mechanisms are probably not involved despite the accentuated humoral immune response and the normal cell-mediated immune responses to measles seen in children with this disease. Evidence now favours the role of mutants of measles virus presumably arising during the primary infection years before (Hall, Kiessling and ter Meulen, 1978; Wechsler and Fields, 1978). The measles variants in subacute sclerosing panencephalitis apparently fail to bud from cells in brain or in cell cultures to produce infectious extracellular virus. Therefore, they avoid clearance by immune responses, yet retain ability to move slowly from cell to cell through fusion.

Progressive multifocal leukoencephalopathy, a rare demyelinating disease due to opportunistic infection with papovaviruses, provides our final and possibly best example of the selective vulnerability of neural cells to viral infections. In this disease the mechanism of the demyelination appears straightforward. JC virus, the major cause of progressive multifocal leukoencephalopathy, is a common human papovavirus; most adults have antibody to JC virus although the virus has not been associated with any other disease (Padgett and Walker, 1976). In the immunosuppressed patient the virus appears capable of causing a lytic infection of oligodendrocytes. Oligodendrocytes are destroyed within the demyelinated foci, and around the foci they are enlarged with nuclear inclusions comprised of papovavirus virions (fig. 5) (ZuRhein, 1969). The virions extracted from the brain do not appear to be defective (Dörries, Johnson and ter Meulen, 1979).

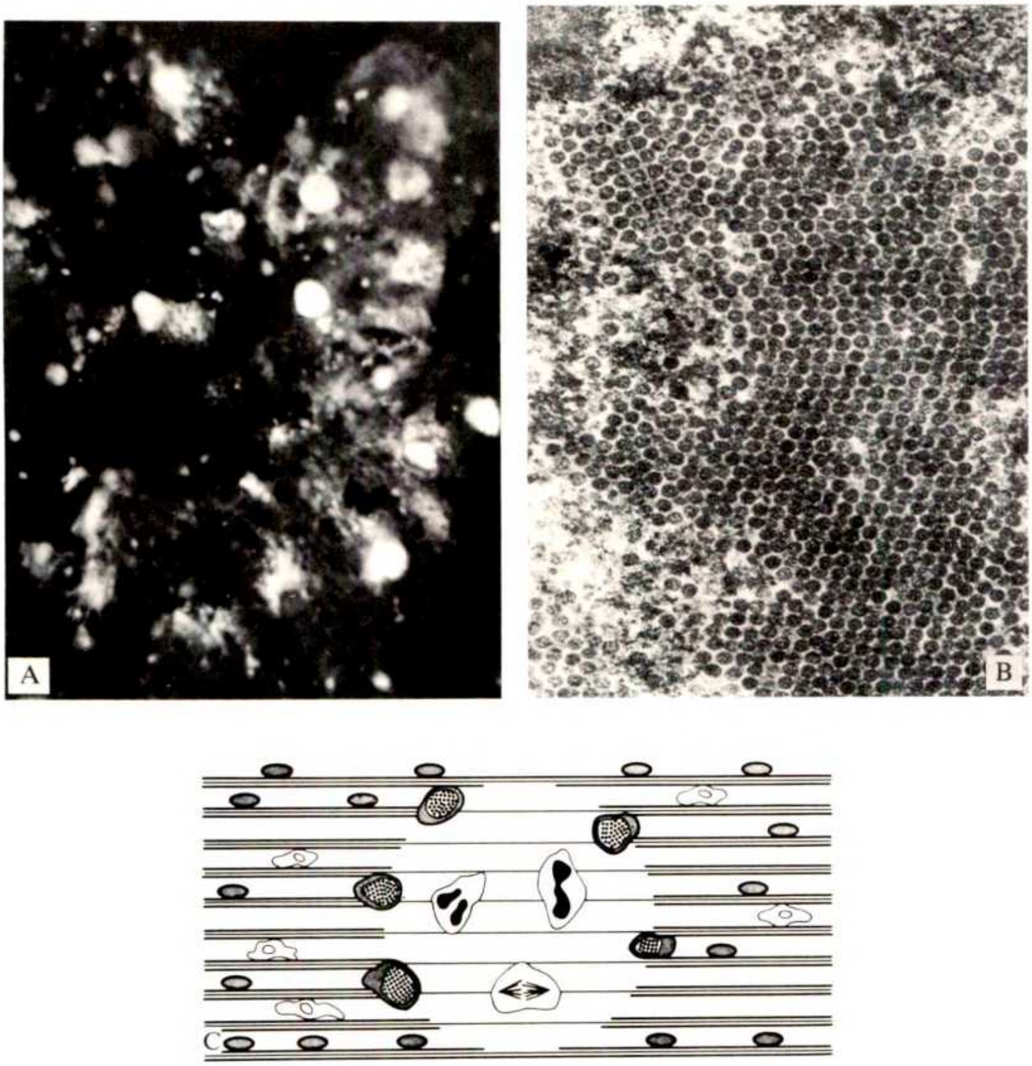

FIG. 5. Progressive multifocal leukoencephalopathy in man. A, fluorescent antibody staining of margin of demyelinated focus (*left*) shows JC virus antigen in enlarged putative oligodendrocytes. × 280. B, electron micrograph of oligodendrocyte nucleus at margin of lesion shows pseudocrystalline arrays of virions. × 48,000. C, schematic diagram of demyelinated lesion. Neurons (not shown) show no evidence of infection and their axons (shown as fine lines) are intact through the lesion. Oligodendrocytes (shaded cells) are absent within the lesion and are enlarged and contain many virions at the periphery; their myelin sheaths are destroyed within the lesion. Astrocytes (clear cells) are normal distant from the lesion but within the lesion are enlarged and may contain multiple nuclei, distorted nuclei and mitotic figures. (Reprinted from Johnson, Narayan and Weiner, 1974.)

In this disease the astrocytes are also abnormal. Within the demyelinated foci astrocytes are enlarged and show abnormal mitotic figures, dumbell-shaped nuclei or multiple nuclei, but only rarely do they contain small numbers of virions. In the original description of this disease they were compared to malignant cells in astrocytomas (Åström, Mancall and Richardson, 1958). The papovaviruses causing progressive multifocal leukoencephalopathy cause brain tumours when inoculated intra-cerebrally into newborn hamsters, JC virus has caused malignant astrocytomas in owl monkeys (London, Houff, Madden, Fuccillo, Gravell, Wallen, Palmer and Sever, 1978), and papovaviruses have been shown to transform or alter growth of astrocytes in cultures of human fœtal brain (Shein, 1967). Furthermore, cells, presumed to be astrocytes, grown from brain of patients with progressive multifocal leukoencephalopathy have been shown to express a nuclear 'tumour' antigen, characteristic of cells transformed by papovaviruses (Weiner and Narayan, 1974). Therefore, in progressive multifocal leukoencephalopathy the principle that different cells may have different susceptibility to different viruses and viruses can have varying effects on host cells seems to be demonstrable within the same organ—neurons appear to be insusceptible, oligodendrocytes are susceptible and lytically infected, and astrocytes are non-permissively infected with morphological alterations suggesting transformation (fig. 5c).

CONCLUSION

I have presented the thesis that the diversity of pathological manifestations of virus infections can be explained by the fact that varied cell populations have different susceptibility to different viruses and that viral infections can have varied effects on host cells. Using examples primarily from studies in our laboratories, variations on this theme have been presented showing how in acute infections selective vulnerability may lead to different clinical symptomatology; how infection of specific cells in the developing nervous system can lead to a variety of malformations such as hydrocephalus, porencephaly, hydranencephaly, or cerebellar hypoplasia; and how the localization and histopathology of virus-induced tumours in animals may be dependent on mitotic activity of the neural cell populations. In the chronic degenerative diseases caused by spongiform encephalopathy agents the hypotheses has been made that a generalized cellular infection may interfere with cell viability and that such an infection would be expected to be expressed first in neurons, the cells of the body with the highest metabolic requirements and the lowest regenerative capacity. However, other mechanisms for spongiform degeneration have been suggested by our studies with a conventional virus, a murine retrovirus, which causes a chronic non-inflammatory spongiform polioencephalomyelopathy. Some of the varied mechanisms by which viruses can cause demyelination have been noted including selective infection of oligodendrocytes or their direct or indirect disruption by immune responses to viral antigens. In progressive multifocal leukoencephalopathy we have seen how in a single organ, the brain, the different cells may be selectively infected by the virus and how the infection can have different effects on different cell populations during the same infectious process.

The diverse pathogenetic potentials of viruses make it possible to speculate that almost any neurological disease of unknown cause could have a viral ætiology. The transmission of familial Creutzfeldt-Jakob disease has shown that even familial degenerative diseases can be caused by a virus-like agent. Furthermore, failures to find viral structures in tissues or to recover viruses with present methods do not eliminate the possible antecedent or ongoing role of infection in the disease.

During the past thirteen years convincing evidence has been accumulated that kuru, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis, progressive rubella panencephalitis and progressive multifocal leukoencephalopathy are of viral ætiology (Johnson and Gibbs, 1974). These findings in human chronic neurological diseases have changed our perspectives but have given us few clues as to what specific diseases may prove to be related to viruses in the coming decades. The recognition of the role of viruses in numerous natural and experimental malformations of animals certainly suggests that some human cerebral anomalies will prove to be of viral ætiology, the role of viruses in some cerebral neoplasms remains a promising possibility, and the establishment of a viral causation for five chronic human degenerative and demyelinating diseases portends that other chronic neurological diseases almost certainly will prove to have a similar pathogenesis.

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FAMILIAL OCULOLEPTOMENINGEAL AMYLOIDOSIS[1]

by HERSHEL GOREN,[2] MARTA C. STEINBERG *and*
GHOLAM H. FARBOODY

(*From The Cleveland Clinic Foundation, Cleveland, Ohio, USA*)

INTRODUCTION

ALTHOUGH the clinical neurological manifestations of familial amyloidosis are almost always confined to the peripheral nervous system, some reports on pathological findings describe amyloid in the leptomeninges. It is surprising, therefore, that the central nervous system is spared clinically. We report on a Hessian (German) family from Ohio (USA) in which the manifestations of dominantly inherited amyloidosis are limited to central nervous and ocular dysfunction: dementia, seizures, strokes, coma and visual deterioration. The cerebrospinal fluid is xanthochromic with lymphocytic pleocytosis and elevated protein.

The fact that amyloidosis may be inherited, generally in autosomal dominant fashion, and that it may have striking neurological manifestations has been known to neurologists since Andrade (1952) reported on Portuguese families with dominantly inherited amyloidotic peripheral neuropathy. Involvement of the peripheral nervous system is common to most of the varieties of familial amyloidosis, but differences in clinical presentation and the distribution and severity of involvement as well as associated affection of other organs (for example, eye and kidney) allow for separation into different types. The basic neuropathological findings in the hereditary amyloidotic peripheral neuropathies also show many similarities in the various kindreds, despite the striking differences in clinical signs and symptoms. It is the location, severity and age of the lesions which vary and apparently account for these differences.

PATIENTS

Case 1 (III 5 in Fig. 1)

A 50-year-old right-handed comatose man was admitted to the Cleveland Clinic Hospital on June 9, 1973 with a twenty-year history of dizziness and a ten-year history of tremor of the right upper limb. Three weeks before admission abnormal gait, forgetfulness and occipital headache had developed. His tremor worsened and once he was unable to speak for several minutes. Right facial paresis appeared one week before admission. On the day before admission the facial weakness increased and left hemiparesis developed. On the morning of admission he vomited and became unconscious.

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[2] Reprint requests: The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106, USA (Dr Goren).

On examination the rectal temperature was 38.3° C; otherwise the results of the general medical examination were normal. He was obtunded and had left hemiplegia and right facial paresis. Muscle stretch reflexes were hyperactive and the left plantar response was extensor. His condition worsened until the third hospital day when he started improving. Examination showed left hemiparesis and hemihypæsthesia, a lesser degree of right hemiparesis and hemihypæsthesia and peripheral right facial paresis. He continued to improve, but with residual left-hemiparetic and ataxic gait and he was discharged on June 28.

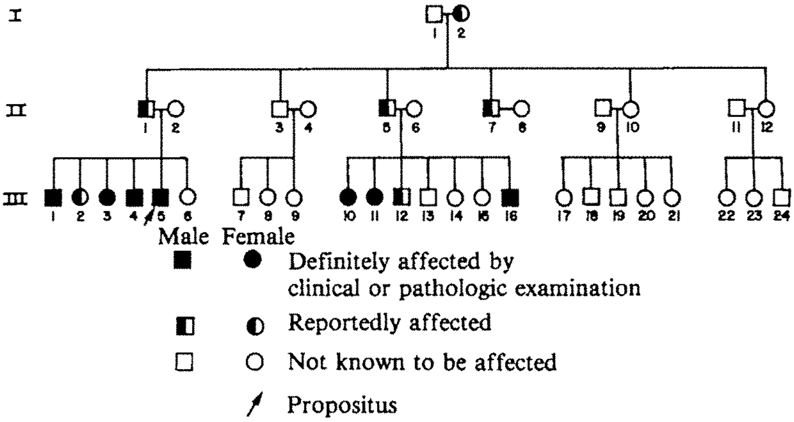

FIG. 1. Pedigree of family.

Lumbar punctures were carried out on the first, second and thirteenth hospital days (Table 1). The electroencephalogram done on the third hospital day showed theta and delta activity bilaterally, temporal sharp complexes and absence of alpha rhythms; the electroencephalograms done on the fourth and fourteenth hospital days were improved. The brain scan and right carotid angiogram were normal. The erythrocyte sedimentation rate and fibrinogen and glycoprotein values were slightly elevated and the antinuclear factor was 1:160; the lupus erythematosus test and latex fixation were negative. The lipid data showed Type IIB hyperlipoproteinæmia (Beaumont, Carlson, Cooper, Fejfar, Fredrickson and Strasser, 1970). The first urine specimen showed 4+ glycosuria; results of the other blood and urine tests were normal. The electrocardiogram and chest x-rays were normal.

The patient was readmitted for a few days in July and again in August 1973 because of alternating episodes of either right hemiparesis, right hemihypæsthesia and aphasia or left hemiparesis and left hemihypæsthesia. Symptoms would progress for minutes to hours and afterwards he might have occipital headache. Serum protein electrophoresis was normal, but immunoelectrophoresis showed the immunoglobulin G to be decreased. The cerebrospinal fluid was less abnormal than previously (Table 1). The electroencephalogram was normal. A right retrograde brachial angiogram and left carotid angiogram were normal upon review by subtraction technique. The glucose tolerance test showed a slightly elevated two-hour value. Blood tests were otherwise unchanged.

The patient had gradually lengthening episodes of hemiparesis and hemihypæsthesia and sometimes speech disturbance, nausea, vomiting, headache and sleepiness with symptoms persisting for hours. Cerebrospinal fluid collected in September 1973 showed improvement (Table 1). In 1975 visual blurring developed and ophthalmological examination showed vitreous opacities which progressively became more dense. (In 1974 ophthalmological examination had been normal.) In addition,

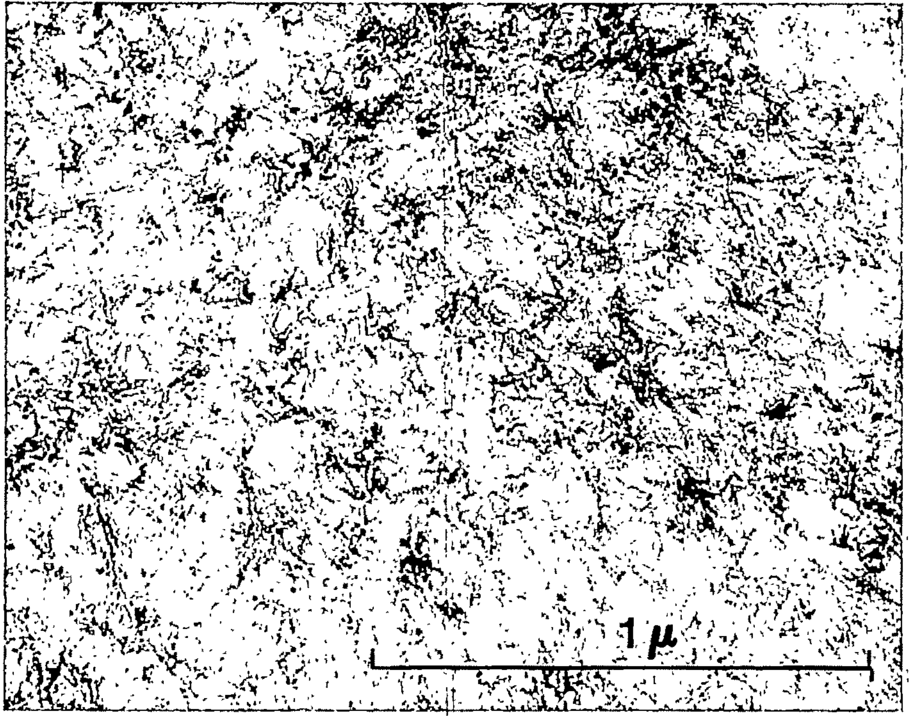

FIG. 2. *Case 2.* Electron micrograph of vitreous aspirate. Lead citrate and uranyl acetate staining.

The patient underwent right vitrectomy in August 1974 and her vision improved. The vitreous contained amyloid (fig. 2).

The patient became progressively demented. She died on June 19, 1975 at the age of 55 years in a nursing home and an autopsy was carried out.

Case 3 (*III 11 in Fig. 1*)

A 57-year-old right-handed woman was found to have vitreous opacities in 1974. Vitreous aspiration, conjunctival biopsy and rectal biopsy all showed amyloid.

She was admitted to hospital in March 1976 because of dementia and uncontrollable behaviour. Her family reported that dementia, hearing loss, visual disturbance and occipital headache had started in 1973. The patient had had generalized seizures for eight months.

On examination the blood pressure was 178/120 mm Hg; otherwise vital signs were normal. The patient was alert but profoundly demented. She had hypertensive retinopathy and vitreous opacities. Peripheral arterial pulses were diminished. The gait was spastic and ataxic. Muscle stretch reflexes were symmetrically hyperactive and the plantar responses were extensor. Limb muscles were minimally weak with atrophy of distal lower limb muscles. Appreciation of pain and touch were diminished distally.

The cerebrospinal fluid data are shown in Table 1. The electroencephalogram showed frontal intermittent rhythmic delta activity, slowed alpha rhythms and few beta rhythms. The radioactive brain scan was normal. Nerve conduction studies and needle electrode examination showed L5 radiculopathy bilaterally. Tests for collagen disease showed no definite abnormalities except that the immunoglobulin A was 13.00 g/l (upper limit of normal 3.4). Results of other blood and urine tests were normal. The electrocardiogram showed non-specific changes. X-rays of the chest and skull were normal.

The patient died on December 7, 1976 at the age of 60 years and an autopsy was carried out.

Case 4 (III 16 in Fig. 1)

A 35-year-old right-handed man had been unable to walk for two weeks in 1967 when a pneumoencephalogram showed a mild degree of cerebral atrophy. He was comatose for seven days afterwards and he awoke with aphasia and right hemiparesis which resolved in weeks. An electroencephalogram showed theta and delta activity in the right temporal region along with diminished physiological rhythms bilaterally. He had three further episodes of right hemiparesis and aphasia and when admitted to the Cleveland Clinic Hospital in 1969, an additional history of episodic violence was obtained. On examination he was lethargic and demented. An electroencephalogram showed theta and delta activity in the left temporal region and ill-defined alpha rhythms on the left. X-rays of the skull and a radioactive brain scan were normal. Results of routine blood and urine tests and a left carotid angiogram were normal. Examination in the Cleveland Clinic Ophthalmology Department in February 1974 showed no vitreous opacity.

The illness which prompted admission on April 12, 1974 started on March 24 with the development of drowsiness and alternating hemiparesis. On March 28 he pulled at his face and hair and seemed to be in pain. He then lost consciousness. He awoke with visual hallucinations which persisted for days. Table 1 shows the results of the cerebrospinal fluid examination done at another hospital. The right carotid angiogram showed a mild degree of stenosis of the internal carotid artery.

General medical examination on April 12 was normal. The patient had fluctuating consciousness, nuchal rigidity and Cheyne-Stokes respirations. The left muscle stretch reflexes were hypoactive or absent. Both plantar responses were extensor. Limb muscles were weaker on the left than on the right.

The results of the cerebrospinal fluid examination are shown in Table 1. On April 16 the electroencephalogram showed theta and delta activity bilaterally and alpha rhythms were absent. On April 25 the electroencephalogram was improved. The radioactive brain scan showed increased uptake on the left and less so on the right. The results of blood and urine tests were unremarkable. X-rays of the chest and skull and an electrocardiogram were normal. When he was visited in a nursing home in March 1976, he was demented and wheelchair-bound. He died on December 23, 1978 at the age of 47 years; no autopsy was performed.

Case 5 (III 1 in Fig. 1)

A 47-year-old right-handed man was admitted to the Cleveland Clinic Hospital in July 1964 with a three-year history of minutes-long episodes of right hemiparesis followed by generalized shaking and sometimes by occipital headache. He would then sleep for hours. On the morning of admission left hemiparesis, left hemihypæsthesia, shaking of the hands, slurred speech, bifrontal headache and obtundation developed. The history included left eye surgery for post-traumatic glaucoma.

On examination the patient was restless and obtunded. He had left hyporeflexia and hemiparesis. Examination of the right eye showed a large vitreous opacity; examination of the left eye showed aphakia and no vitreous opacity.

Table 1 gives the results of cerebrospinal fluid examinations. The first electroencephalogram done on July 7 showed diminished amplitude of right alpha rhythms. The second electroencephalogram done on July 15 showed theta and delta activity bilaterally and poorly developed beta rhythms, less well-developed on the right. The third electroencephalogram done on July 29 showed improvement. The radioactive brain scan, carotid angiograms and pneumoencephalogram were normal. The results of the blood and urine tests were unremarkable. Chest x-rays were normal.

He continued to have episodes of alternating hemiparesis and hemihypæsthesia lasting for hours and nausea and vomiting the next day. Associated with the episodes of right hemiparesis and right facial synkinesis, progressive lethargy, progressive urinary frequency and urgency and bilateral hearing loss developed. The patient received anticonvulsants. He underwent left vitrectomy in February 1976 and his vision improved. Electron microscopy of the vitreous showed amyloid (Cohen and Calkins, 1959).

The patient was readmitted in August 1976 because of two days of progressive right hemiplegia, progressive obtundation and convulsions. Neurological examination showed somnolence, aphasia, right hemiplegia, right hemianopsia, left hemiparesis and right ocular amyloid. Most of the cerebral deficit resolved over several days. The cerebrospinal fluid remained abnormal (Table 1); amyloid could not be detected by electron microscopy of the cerebrospinal fluid. A computed tomogram of the head was normal. The electroencephalogram showed bilateral delta activity and reduced and slowed physiological rhythms with the abnormalities being more marked on the left than on the right. An audiogram showed bilateral sensorineural hearing loss.

Urinary frequency and urgency worsened and the patient underwent prostatectomy in January 1977 with the cystometrogram not showing evidence of neurogenic bladder. He underwent right vitrectomy and his vision improved. His course fluctuated, but overall there was slow progression of neurological deficit. Convulsions continued. Hours-long episodes of neurological dysfunction might be followed by sleepiness and he might vomit upon awakening from this abnormal sleep. The cerebrospinal fluid was abnormal in April 1977 (Table 1). X-ray diffraction analysis of cerebrospinal fluid sediment showed a beta pattern (Eanes and Glenner, 1968). He was readmitted in August 1978 and February 1979 because of more prolonged episodes of neurological dysfunction. Symptoms at the time of the August 1978 admission included objective vertigo, nausea and vomiting and the audiogram showed more right sensorineural hearing loss than before. The electronystagmogram showed absent caloric responses on stimulation of the right ear with other abnormalities suggestive of central dysfunction. The cerebrospinal fluid obtained in August 1978 (Table 1) was not clearly changed. Computed tomograms of the head obtained in August 1978 and February 1979 showed progressive ventricular dilatation. Cystometric evaluation showed the presence of neurogenic bladder. An electroencephalogram obtained in February 1979 was improved and had generalized theta and delta activity with slow alpha rhythms. During this last period in hospital the patient became confused, belligerent and paranoid.

Case 2 (III 3 in Fig. 1)

A 53-year-old right-handed woman was admitted to the Cleveland Clinic Hospital in December 1973, ten days after having been found unconscious. She had awakened three or four days later with right hemiparesis and hemihypæsthesia with incomplete recovery over the next few days. For ten years her vision had been deteriorating. For two years she had been having episodes of speechlessness.

General medical examination showed no significant abnormalities. Neurological examination disclosed that the gait was ataxic and right-hemiparetic. Hyperreflexia and slight weakness were found, more on the right than on the left. The patient had right hemihypæsthesia. Ophthalmological examination showed vitreous opacities.

The glycoprotein value was slightly elevated, but other tests for collagen disease were normal. Type IIB hyperlipoproteinæmia was found. The glucose tolerance test showed a slightly elevated two-hour value. Routine blood and urine tests and x-rays were normal. Non-specific changes appeared in the electrocardiogram. The cerebrospinal fluid was abnormal (Table 1). In the electroencephalogram theta and delta activity appeared in the left temporal region and background rhythms were less well-developed on the left than on the right. The radioactive brain scan showed increased isotope uptake bilaterally. Amyloid was not found in a rectal biopsy.

In January 1974 seizures beginning with paræsthesiæ of the right arm appeared and she was readmitted in May 1974 after having had two convulsions. The cerebrospinal fluid remained abnormal (Table 1). The electroencephalogram showed more left delta activity than previously, left sharp transients and poorly developed left physiological rhythms. The radioactive brain scan was unchanged and the bone marrow was normal.

TABLE 1. CEREBROSPINAL FLUID

Case	Date (date.month.year)	Opening pressure (mm H_2O)	Appearance	Erythrocytes $\times 10^6/l$	Leukocytes $\times 10^6/l$	Lymphocytes (%)	Monocytes (%)	Segmented neutrophils (%)	Macrophages (%)	Protein (mg/l)	CSF/blood glucose (mmol/l)	Other investigations
1	9.6.73	115	Turbid	512	13	—	—	—	—	3200	4.11/6.66	Negative bacterial and fungal cultures.
	10.6.73	240	Turbid and xanthochromic	1100	68	75	7	18	0	1550	6.55/4.88	Negative bacterial, fungal and tuberculous cultures.
	21.6.73	110	Clear and colourless	2	140	99	1	0	0	1700	3.50/7.60	Negative bacterial, fungal and tuberculous cultures. Nonreactive FTA.
	7.8.73	150	Clear and colourless	0	16	100	0	0	0	1280	4.22/3.39	Negative bacterial, fungal and tuberculous cultures. Negative cytology.
	6.9.73	—	—	2	11	92	7	0	1	1080	3 22/4.11	Negative fungal culture.
	20 8.76	—	Clear and colourless	19	1	100	0	0	0	1500	—	—
	11.4.77	120	Clear and colourless	3	1	0	100	0	0	1930	—	—
	11.8.78	90	Clear and colourless	53	1	79	20	0	1	1870	3.94/—	Negative bacterial culture.
2	26.12.73	105	Turbid and xanthochromic	820	22	81	14	5	0	1060	3.77/3.77	Negative bacterial culture. Nonreactive VDRL.
	28.5.74	130	Clear and colourless	1	1	93	7	0	0	1920	3.89/4.44	Negative bacterial and fungal cultures. Normal gamma globulin.
3	11.3.76	210	Clear and xanthochromic	166	1	53	13	30	4	1090	3.00/4.77	Negative bacterial culture.
4	7.3.74	—	—	0	0	—	—	—	—	1620	—	—
	15.4.74	110	Turbid and xanthochromic	710	2	50	0	50	0	1090	3.89/4.11	Negative bacterial culture.
5	7.7.64	—	Clear and xanthochromic	0	0	—	—	—	—	330	—	Negative cytology. Nonreactive VDRL.
	18 7.64	—	Clear and colourless	0	0	—	—	—	—	550	4.88/4.72	Negative bacterial culture Nonreactive VDRL.

FTA = Fluorescent Treponemal Antibody-absorption Test for Syphilis. VDRL = Venereal Disease Research Laboratory Test for Syphilis.

hemihypæsthesia he was often unable to speak, was irritable, his vision was diminished and he was restless. Later in 1964 dementia, euphoria, dysarthria, ataxic gait, left hemiparesis and right hemihypæsthesia developed. The electroencephalogram improved over a period of months. He was described as feeling better in October 1965.

He died on December 31, 1966 at the age of 49 years in another hospital where an autopsy was performed.

Case 6 (III 4 in Fig. 1)

A 47-year-old right-handed man came under observation in 1968. He had a two-week history of abdominal pain and objective vertigo. The gait was ataxic. The electroencephalogram showed diminished alpha rhythms on the left and diminished beta rhythms on the right.

When he was visited in his home in March 1976, it was learned that he had been bedridden since October 1975. An ophthalmologist had reported the diagnosis of ocular amyloidosis. He died at home on November 24, 1977 at the age of 56 years and autopsy was carried out at the Cleveland Clinic.

Case 7 (III 10 in Fig. 1)

A woman who died at the age of 46 years was considered by relatives to have had the familial illness. An autopsy was done at another hospital and subsequently microscopic sections were sent to the Cleveland Clinic Foundation for examination.

Post-mortem Examinations

Cases 2, 3 and 6 underwent complete examination and Cases 5 and 7 underwent partial examination. In each case the cause of death was pulmonary thromboembolism or bronchopneumonia. Atherosclerotic cardiovascular disease was found in Cases 2 and 3. In some cases there were areas of striking segmental narrowing and dilatation of the distal jejunum, the ileum and the entire colon. Infrequent pericollagenous amyloid deposits (Heller, Missmahl, Sohar and Gafni, 1964) were found in small- and medium-sized vessels of the heart, gastrointestinal tract, liver, spleen, pancreas, kidneys, urinary bladder, uterus, adrenals, parathyroids and skin. Amyloid deposition was noted in subserosal and submucosal blood vessels of the stomach, small intestine and colon.

The fresh brains weighed 1.060 to 1.390 kg. The dura appeared normal in every case, but the leptomeninges were strikingly thickened and had a cloudy yellow discolouration throughout while scattered hard, white areas suggesting calcification were seen in Case 6. In Case 3, however, the leptomeninges were pink to tan and opaque instead. The leptomeninges at the base of the brain, on the ventral surface of the brain-stem (fig. 3) and on the dorsal surface of the spinal cord (fig. 4) were particularly severely affected, attaining a thickness of 0.4 to 0.6 cm. A mild degree of generalized cortical atrophy was present in all cases. The major cerebral arteries showed moderately severe atherosclerotic narrowing but were patent. In Case 3 (a hypertensive patient) the arteries showed segmental dilatation typical of hypertensive cerebrovascular disease. Serial 1 cm coronal sections of the brain, sagittal sections of the cerebellum and cross-sections of the brain-stem and spinal cord were normal apart from mild symmetrical dilatation of the ventricular system in every case, and in Case 3 (hypertensive patient) 0.1 to 0.2 cm cystic lesions were seen in the

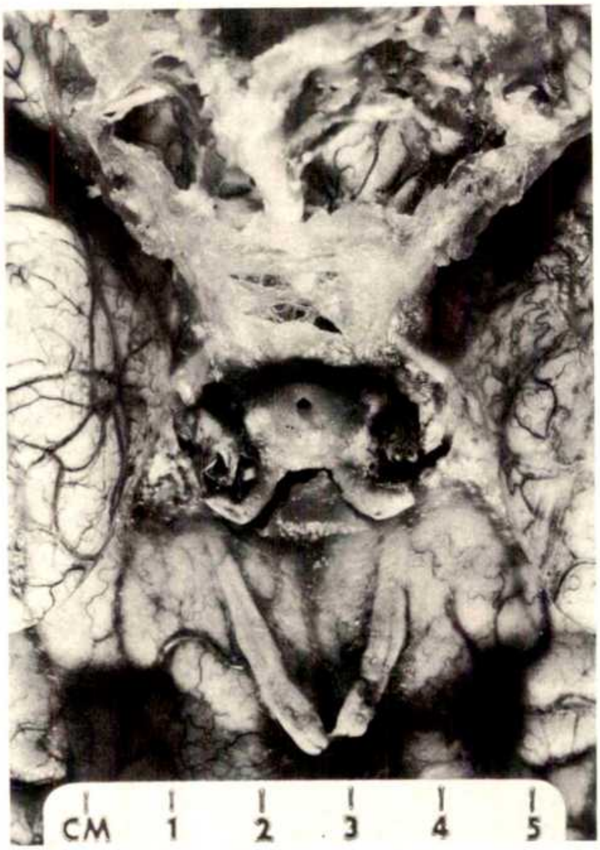

FIG. 3. *Case 2.* Ventral surface of fixed brain. The markedly thickened leptomeninges partially obscure the basilar artery and the cranial nerves.

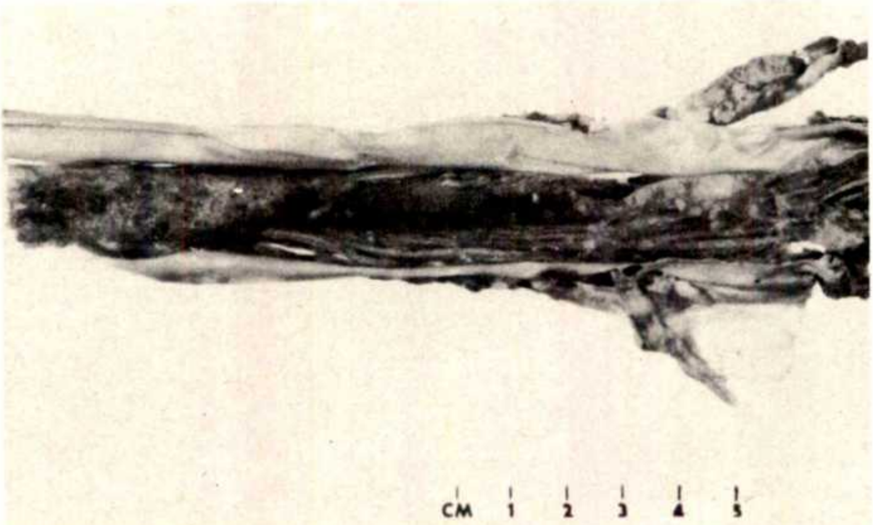

FIG. 4. *Case 2.* Dorsal view of the lumbosacral cord and upper portion of the cauda equina. The dura has been incised and reflected laterally. The thick, opaque leptomeninges cause the dorsal roots to appear matted and ill-defined.

right temporoparietal region, right claustrum, left putamen and cerebellar cortex. Furthermore, in Case 6, sections of the cerebellum showed diffuse, mild thinning of the folia with striking atrophy of the superior vermis, and the ventricular surfaces in every case showed varying degrees of granularity (fig. 5).

Microscopic Pathology

Tissue for light microscopy was fixed in formalin or Zenker's solution, and paraffin or frozen sections were stained with hæmatoxylin and eosin, periodic acid Schiff, Congo red, crystal violet and thioflavin T. Selected sections were stained with phosphotungstic acid hæmatoxylin, Masson trichrome, Klüver (Luxon fast blue-cresyl violet), Bodian, oil red O and Scharlach R. Tissue for electron microscopy from Cases 2, 3 and 6 was fixed in 3 per cent glutaraldehyde followed by 1 per cent osmium tetroxide and embedded in epoxy resin. Ultra-thin sections were examined after staining with lead citrate and uranyl acetate. Examinations were performed with an RCA EMU-4A electron microscope. In all cases amyloid was identified by the characteristic red metachromasia when stained with crystal violet, apple-green fluorescence with Congo red and yellow-green fluorescence with thioflavin T. When material was available for electron microscopy, amyloid was identified by its characteristic straight, nonbranching fibrils with diameter of 5 to 15 nm (Cohen and Calkins, 1959).

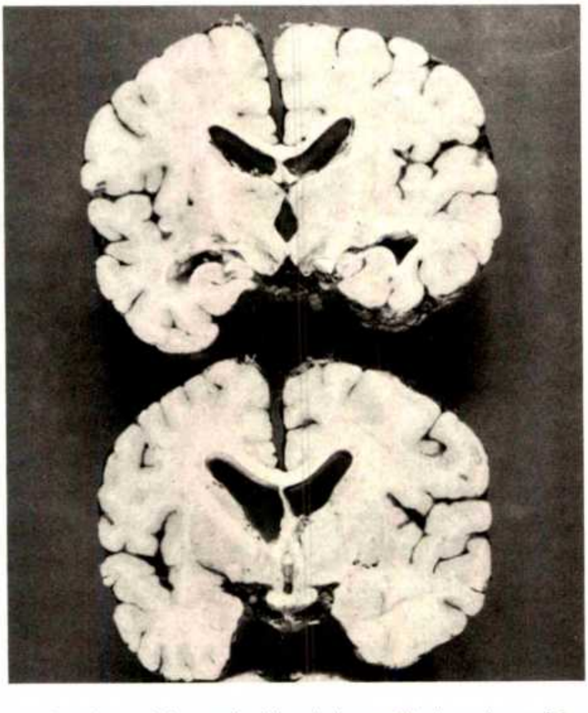

FIG. 5. *Case 6*. Coronal sections of the cerebral hemispheres. The lateral ventricles are mildly dilated.

Cerebral hemispheres and diencephalon. The leptomeninges were markedly thickened because of the presence of amyloid and dense collagen which virtually obliterated the subarachnoid space. Further, there was marked proliferation of arachnoidal cells and a patchy, chronic inflammatory response was present. The subarachnoid blood vessels showed striking changes: pericollagenous amyloid was present in vessels with early involvement, whereas those in the later stages showed replacement of the entire wall by amyloid. Virtually all subarachnoid vessels were affected, but those of small and medium size were more severely involved. Frequently small vessels were occluded (fig. 6) and occasionally had been recanalized. In contrast, after penetration into the parenchyma of the brain the blood vessels no longer contained amyloid, although small, rounded subpial amyloid deposits were noted. The cerebral cortex showed diffuse, extensive neuronal loss which was particularly marked in the superficial layers. Scattered neurons showed acute ischæmic cell changes characterized by bright pink staining with eosin associated with nuclear pyknosis. Similar changes were seen in the pyramidal cell layer of the hippocampus. In Case 6 loss of pyramidal cells in the hippocampus was slightly more marked in Sommer's sector and the end-plate than elsewhere. The cystic lesion in the right temporoparietal region of Case 3 was an old hæmorrhagic infarct and other smaller cortical infarcts, both old and recent, were seen in the right frontal lobe, right occipital lobe and left insula. Old lacunar infarcts

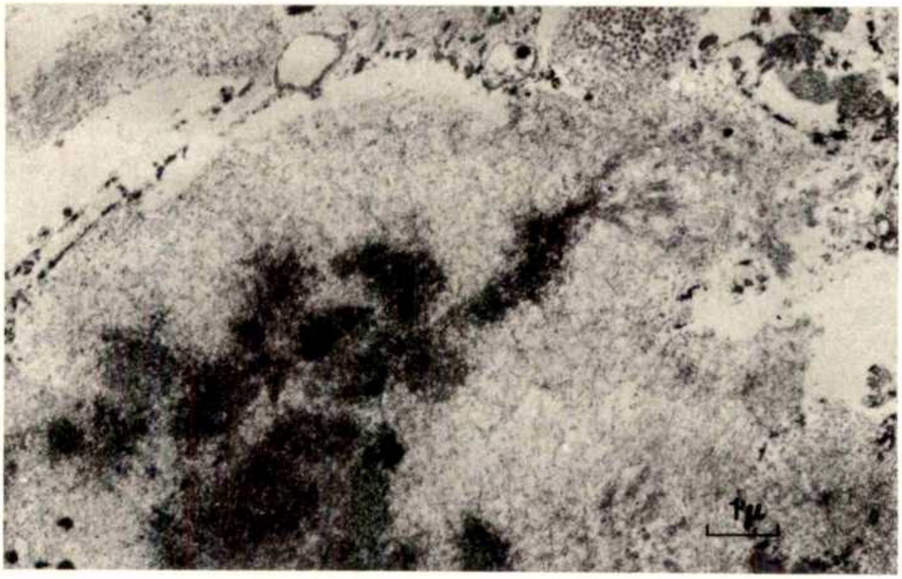

FIG. 6. *Case 3.* Electron micrograph of an occluded small leptomeningeal blood vessel. Lead citrate and uranyl acetate staining. The entire structure is composed of amyloid fibrils surrounding an amorphous osmiophilic core.

were also seen in the left putamen and right claustrum of Case 3. Senile plaques, neurofibrillary tangles and Scholz plaques (Scholz, 1938) were not found. Similarly, Hirano bodies (Hirano, Dembitzer, Kurland and Zimmerman, 1968) and granulovacuolar degeneration were absent from the hippocampus. The vessels in the subcortical white matter were normal. In Case 6 a single remote microinfarct was found in the anterior limb of the internal capsule. There was mild neuronal loss and astrocytosis in the basal ganglia and diencephalon.

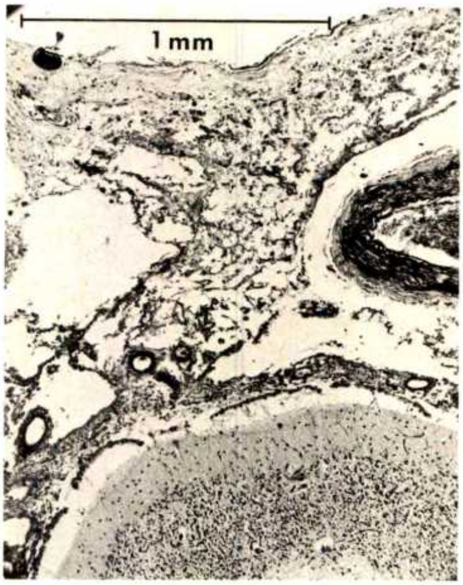

FIG. 7. *Case 2.* Photomicrograph of the cerebellar cortex and overlying leptomeninges. Hæmatoxylin and eosin staining. Note marked thickening of the leptomeninges and loss of Purkinje and granular cells.

Cerebellum. In addition to the leptomeningeal thickening, there was moderate astrocytosis and marked patchy degeneration of the molecular, granular and Purkinje cell layers (fig. 7), and on the axons of the latter there were frequent torpedoes. There was mild neuronal loss in the dentate nucleus and both astrocytosis and microglial proliferation were more prominent here than in the cerebellar cortex. In Case 3 there were scattered small old and recent infarcts noted throughout the cerebellar cortex. In Case 6 the superior vermis was more atrophic than other parts of the cerebellum and sections of the superior vermis confirmed the presence of more marked changes here than elsewhere; these changes suggested superimposed nutritional deficiency.

Brain-stem. In sections of midbrain, pons and medulla there was extensive subpial gliosis and the overlying leptomeninges showed changes similar to those seen elsewhere. The pigmented nuclei showed no significant pigment incontinence or specific neuronal changes. The inferior olivary, vestibular and auditory nuclei showed neuronal degeneration and reactive astrocytosis and a few scattered foci of neuronophagia and microglial scars. In Case 3 the acoustic nerve roots contained amyloid deposits both interstitially and in the blood vessels of the perineurium. Microglial nodules were seen in the inferior olivary nucleus of Case 6 and were thought to be secondary to the cerebellar abnormalities and in this case there was no other evidence of nutritional deficiency.

Ventricular system. There were numerous ependymal granulations containing large deposits of amyloid with focal denuding of the ependymal surface and proliferation of subependymal astrocytes (fig. 8). Mild, chronic perivascular inflammation was seen around the subependymal blood vessels. Many subependymal blood vessels contained amyloid.

Spinal cord. Enormous amounts of amyloid were deposited in the markedly fibrotic spinal leptomeninges and in the associated blood vessels, many of which were occluded; scattered foci of metaplastic bone formation had developed within the spinal leptomeninges. The spinal roots and ganglia showed mild, patchy perineurial amyloid deposits. Extensive subpial degeneration and gliosis were recognized throughout the spinal cord, particularly in the posterior columns and the root entry zones. No significant abnormalities were seen in the anterior horn cells.

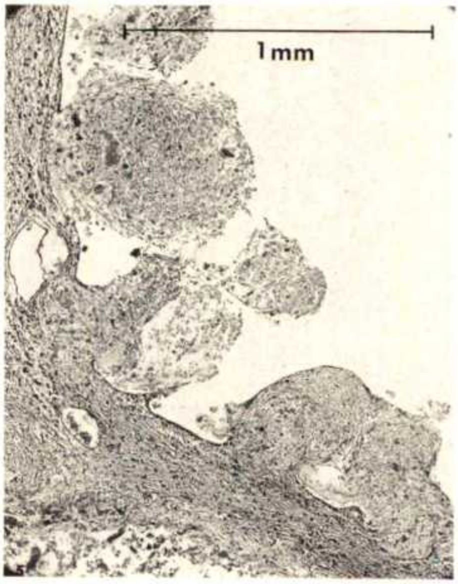

FIG. 8. *Case 6.* Photomicrograph of the surface of the fourth ventricle. Hæmatoxylin and eosin staining. Proliferation of subependymal astrocytes with amyloid deposits on the ventricular wall have caused striking ependymal granulation.

Vitreous, retina and optic pathways. The eyes were examined in Case 2. The central retinal vessels showed minimal amyloid deposition. Amyloid was seen in the superficial retinal layers with frequent amyloid deposits within the nerve fibre layer, the internal limiting membrane and the vitreous. Although there was mild loss of ganglion cells and their fibres, there were no other significant pathological changes in the retina. In the optic nerve sheath there were pathological changes similar to those seen in the leptomeninges; in addition, there was loss of nerve fibres, isomorphic gliosis and thickening of the connective tissue septa of the optic nerve, most striking at the periphery. The optic chiasm and optic tracts showed changes similar to those seen in the optic nerve. Moderate neuronal loss and astrocytosis were seen in the lateral geniculate bodies.

Peripheral nerves. A mild dying-back polyneuropathy was seen in the nerves sampled (Table 2), but amyloid was found only infrequently in intraneurial blood vessels. Rarely perineurial vascular amyloid deposition was seen. One small infarct was found in a sciatic nerve of Case 3, but otherwise there were no abnormalities related to vascular changes.

Skeletal muscles. Denervation atrophy was recognized in all muscles sampled. A mild degree of vacuolar myopathy was found in Case 3. Amyloid-containing blood vessels were found infrequently.

DISCUSSION

Although de Bruyn and Stern's (1929) case of Dejerine-Sottas disease really had familial amyloidotic peripheral neuropathy (De Navasquez and Treble, 1938), it was Andrade (1952) who popularized this diagnosis when he reported Portuguese families with a stereotyped clinical picture of disabling peripheral neuropathy. In retrospect, Freitas Julião and Couceiro (1940) and Wohlwill (1942) described the same entity and Freitas Julião subsequently restudied one of his cases to confirm this (Freitas Julião and Mignone, 1955). Amyloid-bearing tissues from such patients contain what appears to be a unique protein closely related to normal human serum prealbumin (Costa, Figueira and Bravo, 1978).

Rukavina, Block, Jackson, Falls, Carey and Curtis (1956) described amyloidosis in a Swiss family living in Indiana whose nondisabling neuropathy started with symptoms of the carpal tunnel syndrome. A similar neuropathy has been described in a German family living in Maryland by Schlesinger, Duggins and Masucci (1962) and in greater detail by Mahloudji, Teasdall, Adamkiewicz, Hartmann, Lambird and McKusick (1969). One member of the Maryland family had seizures (Kaufman and Thomas, 1959).

Other descriptions of familial amyloidosis with neurological features include a Scottish-English-Irish family living in Iowa whose members had neuropathy and in whom uræmia was the commonest cause of death (Van Allen, Frohlich and Davis,

TABLE 2. PATHOLOGICAL FINDINGS IN THE CRANIAL AND SPINAL ROOTS AND GANGLIA AND IN THE PERIPHERAL NERVES

	Case 2	*Case 3*	*Case 5*	*Case 6*	*Case 7*
Structures examined	Trigeminal nerve root and ganglion; spinal roots and sensory ganglia; brachial and lumbosacral plexuses; and radial, femoral, sciatic, peroneal and sural nerves	Acoustic nerve root and ganglion; spinal roots and sensory ganglia; brachial plexus; and ulnar, femoral, sciatic, peroneal and sural nerves	Not examined	Spinal roots and sensory ganglia; brachial plexus; and ulnar, femoral, sciatic and sural nerves	Not examined
Perineurial vascular amyloid	Patchy, mild	Acoustic nerve root, moderate; all others, mild	Not examined	Patchy, moderate	Not examined
Perineurial interstitial amyloid	Patchy, mild	Acoustic nerve root, moderate; all others, mild	Not examined	Patchy, moderate	Not examined
Endoneurial vascular amyloid	Absent	Acoustic nerve root, moderate; all others, absent	Not examined	Patchy, mild	Not examined
Endoneurial interstitial amyloid	Absent	Acoustic nerve root, moderate; all others, absent	Not examined	Patchy, mild	Not examined
Infarction of nerve	Absent	Sciatic nerve, remote small infarct; all others, absent	Not examined	Absent	Not examined
Nerve fibre loss	Trigeminal nerve root and ganglion, mild; all others, moderate dying-back polyneuropathy	Acoustic nerve root and ganglion, moderate; all others, moderate dying-back polyneuropathy	Not examined	Severe dying-back polyneuropathy	Not examined

1969), a Swedish family living in the United States whose members had disabling peripheral neuropathy and renal failure (Benson and Cohen, 1977) and Finnish patients with lattice dystrophy of the cornea, progressive cranial paralysis and then peripheral neuropathy (Meretoja and Teppo, 1971).

Involvement of the eyes has become apparent as more cases of familial amyloidosis have been studied. Irregular, unequal pupils with diminished reaction to light and convergence was reported by de Bruyn and Stern (1929), De Navasquez and Treble (1938), Freitas Julião and Couceiro (1940) and Andrade (1952). A postganglionic sympathetic disturbance probably causes most of the pupillary abnormalities (Okajima, Nagata, Hatamoto, Kinoshita, Takaba and Tokuomi, 1978). Kantarjian and DeJong (1953) reported vitreous opacities and Kaufman (1958) demonstrated that the vitreous opacities do indeed contain amyloid.

Varying amounts of amyloid have been found in the leptomeninges of cases of familial and apparently nonfamilial amyloidosis, but generally these deposits have been considered clinically insignificant (De Navasquez and Treble, 1938; Fisher and Preuss, 1951; Ritama and af Björkesten, 1954; Chambers, Medd and Spencer, 1958; Van Allen *et al.*, 1969; Meretoja and Teppo, 1971; Benson and Cohen, 1977). Thickening of the leptomeninges of the brain and spinal cord and infiltration of meningeal vessels with amyloid have been reported in Portuguese neuropathy (Freitas Julião and Couceiro, 1940; Silva Horta, 1955; Silva Horta and Dias Coelho, 1960; Silva Horta and Trincâo, 1963; Silva Horta, Filipe and Duarte, 1964; Delank, Koch, Könn, Missmahl and Suwelack, 1965; Freitas Julião, Queiroz and de Faria, 1974; Hofer and Andersson, 1975).

Haberland (1964) described a woman with ataxia, tremor, psychosis, confusion and stupor. Pathological examination of the atrophic brain showed ependymal, leptomeningeal and subpial deposition of amyloid with occasional involvement of the superficial layers of the cortex. In contrast to our cases, Haberland's case showed Congophilic angiopathy (Pantelakis, 1954), plaque-like angiopathy (Scholz, 1938) and senile plaques.

Silva Horta *et al.* (1964) found an area of cerebral infarction caused by amyloidotic occlusion of a blood vessel in a case of Portuguese amyloidotic peripheral neuropathy and they claimed there is no other generalized amyloidosis with such great deposits of amyloid surrounding the central nervous system. Krücke (Götze and Krücke, 1941; Case 1 of Krücke, 1950) described one patient with sporadic amyloidotic neuropathy who also had loss of memory and a personality change. At autopsy this patient had amyloid deposition in leptomeningeal blood vessels causing granular atrophy of the cortex and infarcts. Another patient (Case 2 of Krücke, 1950) had syphilis, peripheral neuropathy, hypersomnia, nausea, vomiting and seizures. Amyloid was found in the leptomeninges at autopsy.

We are aware of only two other families (from the Netherlands and from Japan) afflicted with familial oculoleptomeningeal amyloidosis with disabling central nervous dysfunction. Hamburg (1971) reported three siblings with progressive visual deterioration caused by vitreous amyloid deposition and briefly described neurological manifestations. In the first sibling progressive neurological dysfunction prompted laminectomy and circumscribed arachnoiditis was found. Subsequently disorientation, vomiting and muscular atrophy developed. The second sibling had ataxia, pathological reflexes, seizures, obtundation, Cheyne-Stokes respirations, incontinence, muscular atrophy, vomiting and hiccoughs. Autopsy on this individual showed amyloid deposition in the leptomeninges encircling the medulla. Amyloid penetrated inside the marginal zone of the brain. Less abundant amyloid was found on examination of the spinal cord. Amyloid was present in the eyes. Foci of amyloid were found in nerve roots, ganglia and plexuses and less amyloid was found in various organs.

Writing first in Japanese and then in English, Okayama and associates (Okayama, Goto, Tanaka and Omae, 1974; Inomata, Okayama and Oshima, 1976; Okayama, Goto, Ogata, Omae, Yoshida and Inomata, 1978) described in detail a family with amyloidosis, central nervous dysfunction and vitreous opacities. They studied nine patients, one of whom had come to autopsy, with amyloidosis inherited in autosomal dominant fashion and without clinical evidence of peripheral neuropathy. From the age of 24 to 35 years decreased libido, visual symptoms and hearing loss developed in the propositus. Recurrent nausea, vomiting, dizziness, abdominal pain and grossly abnormal behaviour then developed and he would lose consciousness for hours at a time. At the age of 36 paræsthesia of both arms appeared, at the age of 38 he had an episode of loss of consciousness and right hemiparesis and three months later, delirium and visual hallucinations developed. On examination at the age of 38 years he had oval, unequal, poorly reactive pupils, questionable nuchal rigidity, tremor and unsteady, slow gait. There was no clinical evidence of peripheral neuropathy, but motor nerve conduction velocities were slightly slowed. The cerebrospinal fluid, under normal pressure, was xanthochromic with a normal cell count and a protein of 4,600 mg/l. Both the isotope cisternogram and the myelogram showed thoracic arachnoid adhesions. Enlargement of the lateral ventricles appeared on the pneumoencephalogram. Recurrent aphasia, delirium and right hemiplegia and then involuntary movements of the left limbs developed. A convulsion occurred. Autopsy showed bilateral cerebral infarcts and thickening of the leptomeninges with obliteration of the spinal subarachnoid space. In the leptomeninges amyloid was deposited in the adventitia of the arteries and diffusely throughout the walls of the arterioles and veins. The vessels became free of amyloid shortly after piercing the pia. Beneath the pia the amyloid formed continuous patches that extended into the molecular layer of the cerebral cortex and the fibre tracts of the brain-stem and spinal cord. Subependymal amyloid was not seen. The Gasserian, sympathetic and parasympathetic ganglia showed amyloid deposition in vessel walls and perivascular structures with slight loss of neurons. Demyelination and loss of axis cylinders were recognized in the femoral nerve. Amyloid deposition was found in the vitreous and other ocular structures. The vitreous amyloid seemed to originate from deposition in retinal blood vessels which penetrated through the basement membrane of the inner limiting membrane. Neuronal degeneration in the retina was thought to be severe enough to have caused the visual disturbance. Lesser amounts of amyloid were recognized in other organs.

In the present family signs of motor, sensory, intellectual, speech and visual impairment have developed in affected individuals, often with seizures or intermittent obtundation, in the fourth, fifth or sixth decade, but in some cases our historical information is incomplete (Table 3). Although the overall course of the disease is progressive, we are impressed with the episodic nature of neurological dysfunction and we speculate that such episodic dysfunction results from transient cortical ischæmia. Small, superficial cortical infarcts resulting from occluded subarachnoid vessels could cause the seizures. Members of this family often have slowly progressive obtundation, on occasion associated with headache. We are tempted to attribute the obtundation and headache to intermittent hydrocephalus with the amyloid-laden leptomeninges absorbing cerebrospinal fluid poorly. We did not find evidence of marked hydrocephalus when we studied comatose patients by computed tomography, angiography, or pneumoencephalography, but we did find evidence of hydrocephalus on pathological examination of some cases. We speculate that in affected individuals an abnormal protein present in relatively high concentration in the cerebrospinal fluid precipitates on to surfaces bathed by the cerebrospinal fluid. We liken this to the unique protein closely related to normal human serum prealbumin found in tissues of individuals afflicted with Portuguese familial amyloidotic polyneuropathy (Costa *et al.*, 1978). Prealbumin is concentrated in cerebrospinal fluid relative to serum and a major fraction of the prealbumin molecule possesses a beta structure, as does amyloid. The capillaries of the normal central nervous system, with the exception of those in the floor of the third ventricle and the area postrema, possess endothelial tight junctions which provide an anatomical barrier to the passage of macromolecules from the bloodstream to the central nervous system parenchyma. Brightman and Reese (1969) showed that intravenously injected type VI horseradish peroxidase did not cross the endothelial tight junctions to enter the brain. We speculate that this characteristic of central nervous capillaries may play a role in preventing the passage of amyloid precursor macromolecules into the intercellular space of the central nervous system, thus accounting for the uniform absence of amyloid from the central nervous parenchyma. In all adequately studied cases we found evidence of dementia. We believe that the superficial pseudolaminar necrosis and the extensive, diffuse cortical neuronal loss would explain such dementia and the abnormal behaviour. Most affected individuals have had vitreous opacities, aspiration of which improved vision. In the present series death has occurred in the fourth or fifth decade with individuals having been symptomatic usually for three to twelve years. However, we are continuing to follow one patient who has been symptomatic for twenty-six years. Further, members of this family report that one individual (I 2 in fig. 1) survived to the age of 68 and another (II 1 in fig. 1) survived to the age of 64 years.

TABLE 3. SUMMARY OF CLINICAL DATA

	Consciousness	*Mental state*	*Seizures*	*Headache*	*Vision*	*Cranial nerves*	*Motor*	*Sensation*	*Speech*	*Medical illnesses*
Case 1. 56-year-old male. 26-yr history. Alive	Coma	Decreased memory and confusion	Generalized	Yes	Vitreous opacities and right hemianopsia	R. facial paresis, decreased hearing, vertigo and absent caloric response on R.	Tremor, bilat. weakness and spastic ataxic gait	Decreased bilat.	Mutism or aphasia	Type IIB hyperlipoproteinæmia and diabetes
Case 2. Died aged 55 yrs. Female. 12-yr history	Coma	Dementia	R. limbs and then generalized	No	Vitreous opacities	Normal	Bilat. weakness and R. hemiparetic and ataxic gait	Decreased on R.	Mutism	Type IIB hyperlipoproteinæmia, diabetes and abnormal EKG
Case 3. Died aged 60 yrs. Female. 3-yr history	Normal	Dementia and rages	Generalized	Yes	Vitreous opacities	Decreased hearing	Spastic ataxic gait and distal atrophy	Decreased distally	Normal	Hypertension, arteriosclerosis and abnormal EKG
Case 4. Died aged 47 yrs. Male. 12-yr history	Coma	Violence, dementia and visual hallucinations	None	Yes	Normal	Normal	Bilat. weakness	Normal	Aphasia	None
Case 5. Died aged 49 yrs. Male. 5-yr history	Obtundation	Irritability, dementia and euphoria	None	Yes	Vitreous opacity	Normal	Tremor, bilat. weakness and ataxic gait	Decreased bilat	Mutism or slurred speech	None
Case 6. Died aged 56 yrs. Male. 9-yr history	Normal	Normal	None	Yes	Vitreous opacities	Vertigo	Ataxic gait	Normal	Normal	None
Case 7. Died aged 46 yrs. Female	—	—	—	—	—	—	—	—	—	—

We carried out pathological examinations on five affected individuals and the neuropathological findings can be summarized as follows (Tables 2 and 4):

(1) the hallmark of the disease is extensive, severe amyloidosis of the leptomeninges and the subarachnoid blood vessels. In two cases this was associated with a granulomatous giant cell reaction, whereas the others showed simple, chronic perivascular inflammation. Large deposits of amyloid and proliferation of fibrous connective tissue in the leptomeninges obliterated the subarachnoid space. The subarachnoid amyloid deposition was diffuse but was greatest along the base of the brain and the posterior and lateral surfaces of the spinal cord. Calcification and metaplastic bone formation were often found in the spinal leptomeninges. The subarachnoid vessels, particularly small- and medium-sized arteries and veins, showed extensive deposition of amyloid throughout the vascular walls with frequent narrowing or occlusion of the lumina. The vascular amyloid disappeared as the vessels penetrated into the parenchyma of the central nervous system;

(2) in all adequately studied cases the ventricles were symmetrically enlarged to a mild or moderate degree and the ventricular surfaces showed patchy, but extensive, amyloid deposition with resulting ependymal granulations, subependymal spongy degeneration and gliosis. The subependymal vessels contained small amounts of amyloid and there was mild, chronic perivascular inflammation;

(3) in all cases we found severe, diffuse neuronal loss which was most marked in the cerebral cortex and cerebellar cortex. Although the superficial cerebral cortical layers were most severely affected, significant neuronal loss was seen in all layers. The cerebellum showed patchy, spongy changes in the molecular layer, varying degrees of granular cell and Purkinje cell loss and active degeneration with occasional swollen axons (torpedoes);

(4) diffuse subpial degeneration and gliosis affecting the white matter was present in all cases;

(5) superficial cerebral and cerebellar infarcts of varying sizes and ages were found in three patients, but one of these also had hypertensive cerebrovascular disease;

(6) senile plaques, neurofibrillary tangles, granulovacuolar degeneration and Hirano bodies were absent in all cases. We found no Congophilic angiopathy;

(7) the tela choroidea and choroid plexus blood vessels showed amyloid deposition;

(8) the spinal roots and the cranial nerve roots and ganglia, particularly the trigeminal and acoustic roots, showed occasional vascular and interstitial amyloid deposits. Similar but less frequent amyloid deposits were seen in the peripheral nerves examined with a mild dying-back peripheral neuropathy.

SUMMARY

Members of a German family living in Ohio (United States) have been found to have dominantly inherited amyloidosis causing dementia, seizures, strokes, coma and visual deterioration. Pathological examination of affected individuals has

TABLE 4. PATHOLOGICAL FINDINGS IN THE CENTRAL NERVOUS SYSTEM

Neuropathological findings	*Case 2*	*Case 3*	*Case 5*	*Case 6*	*Case 7*
Amyloid in the subarachnoid vessels and leptomeninges	Profuse	Profuse	Profuse	Profuse	Profuse
Granulomatous or chronic perivascular changes in the leptomeninges	Mild chronic inflammation	Mild chronic inflammation	Moderate chronic inflammation	Mild chronic inflammation	Profuse granulomatous inflammation
Arachnoidal proliferation and patchy leptomeningeal fibrosis	Extensive	Extensive	Extensive	Moderate	Extensive
Subpial amyloid deposits	Present	Present	Present	Present	Present
Subpial gliosis and degeneration	Extensive	Extensive	Extensive	Extensive	Extensive
Intracerebral parenchymal or vascular amyloid	Absent	Absent	Absent	Absent	Absent
Perivascular demyelination	Absent	Absent	Absent	Absent	Absent
Ependymal amyloid deposits	Moderate	Extensive	Moderate	Extensive	Moderate
Superficial cortical pseudolaminar or focal neuronal loss and astrocytosis	Moderate	Extensive	Extensive	Moderate	Extensive
Diffuse cortical neuronal loss and astrocytosis	Moderate	Moderate	Moderate	Moderate	Moderate
Cerebral cortical infarcts	Absent	Present*	Absent	Absent	Present
Senile plaques and neurofibrillary tangles	Absent	Absent	Absent	Absent	Absent
Diffuse cerebellar cortical atrophy	Present	Present	Present	Present**	Not examined

* Known hypertensive with severe vascular disease. Lacunar infarcts in addition to cortical infarcts.

** Superior cerebellar degeneration also present, probably on a nutritional basis.

shown severe, diffuse amyloidosis of the leptomeninges and subarachnoid vessels associated with patchy fibrosis and obliteration of the subarachnoid space. Amyloid deposits were prominent on the ependymal surfaces and severe and diffuse neuronal loss and generalized subpial gliosis were found in the cerebrum and cerebellum. On occasion superficial brain infarcts were seen. Amyloid was also found in the vitreous, the retinal internal limiting membrane and the retinal vessels, particularly those in the nerve fibre layer. There was only minimal amyloid elsewhere.

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DYSTROPHIA MYOTONICA AND MYOTONIA CONGENITA CONCURRING IN ONE FAMILY

A CLINICAL AND GENETIC STUDY

by C. J. HÖWELER, H. F. M. BUSCH, L. F. BERNINI,
E. VAN LOGHEM, P. MEERA KHAN *and* L. E. NIJENHUIS

(*From the Department of Neurology, Academic Hospital, Rotterdam, the Department of Human Genetics, University of Leyden, and the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands*)

INTRODUCTION

DYSTROPHIA myotonica in its early stage may resemble myotonia congenita, when myotonia is still the only sign and weakness is not yet present. In the past this gave rise to doubts about the distinct nature of the two diseases, especially after 'intermediate forms' had been described (Maas and Paterson, 1939, 1950; Caughey, 1958, 1968). The concept of a continuum of myotonic diseases was vividly discussed, but later the argument subsided and the problem remained unsolved for lack of other than clinical evidence. Most authors accepted the view that the clinical pictures of the two diseases show so many fundamental differences that it is impossible to conceive them as arising from the same genetic defect (Bell and Martin, 1947; Thomasen, 1948; Klein, 1958; Harper, 1979). In view of the far better prognosis of myotonia congenita the question is of practical importance for genetic counselling.

We had the opportunity to study a unique family, consisting of the offspring of a marriage between a woman who was probably a heterozygote for dystrophia myotonica and a man who probably had myotonia congenita. Two of their 5 children had dystrophia myotonica and 3 had myotonia congenita. The two diseases were transmitted independently to the next generations. The first aim of this study is to report the clinical features of the two diseases observed in this family.

Dystrophia myotonica is the first human disease of which linkage to an autosomal marker gene became known. Its linkage with ABO secretor status (Se) and the blood group Lutheran (Lu) was suspected by Mohr (1954) and has since been confirmed by Renwick, Bundey, Ferguson-Smith and Izatt (1971) and Harper, Rivas, Bias, Hutchinson, Dyken and McKusick (1972). The meiotic distance between the

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dystrophia myotonica gene (*Dm*) and the *Se* gene has been estimated to be about 10 centimorgans, which means the recombination frequency between these genes is about 10 per cent. Also, between the *Se* and *Lu* a distance of slightly more than 10 centimorgans was measured. The sequence of the genes on the chromosome appears to be *Dm–Se–Lu*, since the percentage of recombination between *Dm* and *Lu* appears to be about 20 per cent.

The second aim of this study was to find out whether similar linkage exists between the locus for myotonia congenita (*Mc*) and *Se* and *Lu* or whether the *Mc* gene segregates independently from *Se* and *Lu*. An exclusion of similar linkage may prove that the conditions Dm and Mc are determined by genes at separate loci.

THE FAMILIES

The pedigree of the family is shown in fig. 1. During a study of family ST, dystrophia myotonica was diagnosed in a woman (ST III-15) and myotonia congenita in her cousin (ST III-11). Both said that their cramp disease had been present in their grandfather (T I-3). However, we had already found dystrophia myotonica in relatives of their grandmother (S I-4). We therefore studied both the families of the grandfather and of the grandmother, and the offspring of their marriage.

Altogether the study covered 80 individuals, 79 of whom were examined personally: 19 descendants of two sibs of the grandmother S I-4, one living sister and 30 descendants of two brothers of the grandfather T I-3, and 29 first degree relatives in family ST. Adequate medical records were available of one deceased relative (S II-7).

METHODS

All relatives received a general physical and neurological examination and in most of them electromyography was performed as well as slit-lamp examination of the eye lenses.

Dystrophia myotonica can be distinguished from myotonia congenita by the finding of two signs not present in myotonia congenita: muscle weakness and myotonic cataracts (Klein, 1958). The age of onset of dystrophia myotonica varies widely and may even be above the age of 70 years. Subclinical cases can best be detected by combining neurological examination, electromyography and slit-lamp examination of the eye lenses (Bundey, Carter and Soothill, 1970; Polgar, Bradley, Upton, Anderson, Howat, Petito, Roberts and Scopa, 1972).

In myotonia congenita the two characteristic signs, myotonia and muscle hypertrophy, are the most marked in young adults. However, myotonia may be absent (Birt, 1908) or may be so mild as to be clinically detectable only on specific occasions such as cold weather. Therefore, electromyography was also performed.

Neurological Examination

Active myotonia was looked for in the hands and eyelids, and percussion myotonia in the tongue and thenar muscles. Weakness was accepted as a diagnostic sign only if it was found in muscle groups known to be involved most frequently in dystrophia myotonica: the facial, jaw, palatal, neck and distal limb muscles. Equivocal signs such as mild atrophy of temporal and hand muscles were disregarded, as were signs present in many other conditions such as frontal balding, acrocyanosis or cardiac arrhythmia. Signs difficult to distinguish from normal variations such as muscle hypertrophy or

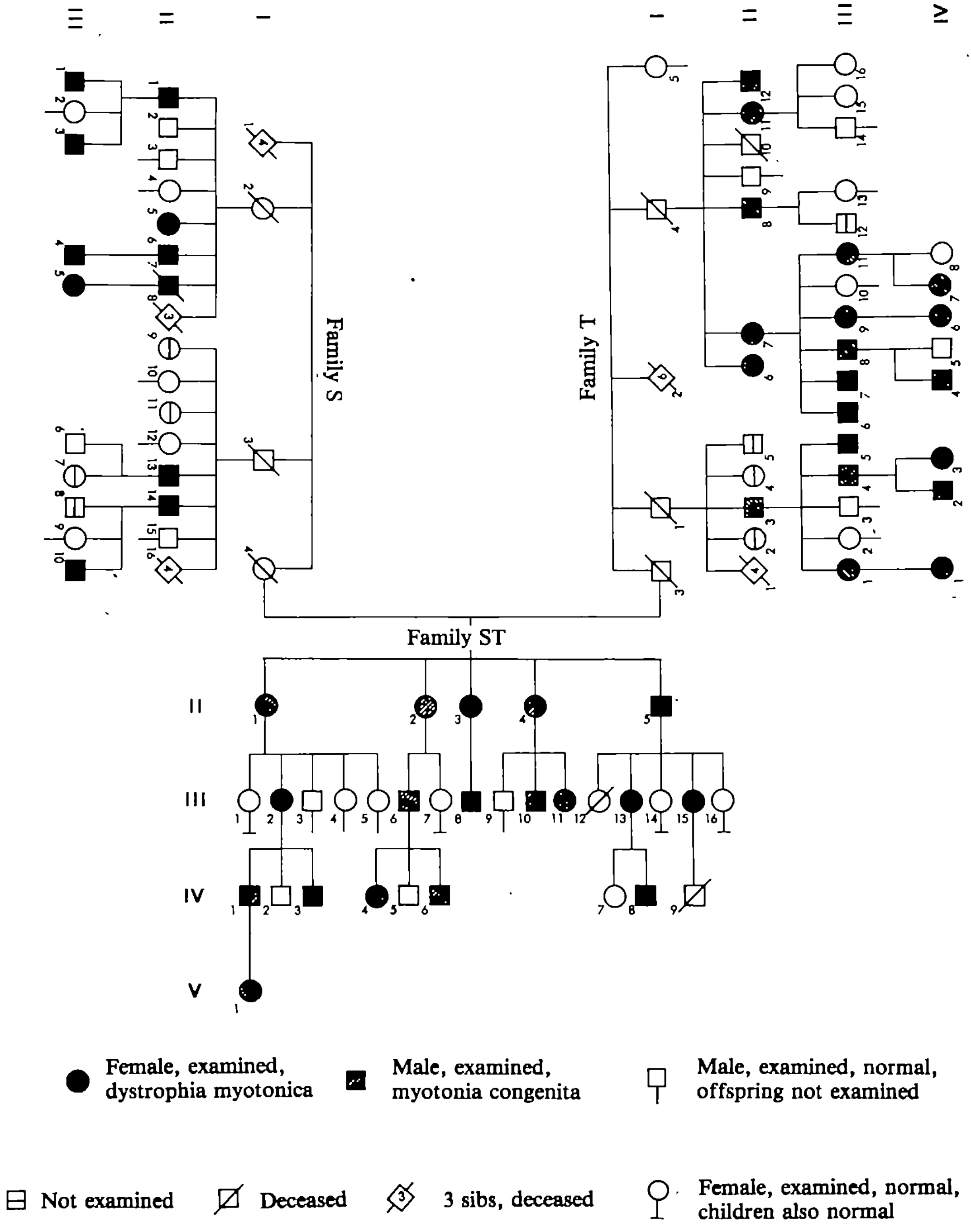
Family S
Family T
Family ST
I
II
III
IV
V
Female, examined, dystrophia myotonica
Male, examined, myotonia congenita
Male, examined, normal, offspring not examined
Not examined
Deceased
3 sibs, deceased
Female, examined, normal, children also normal

FIG. 1. Pedigree tree of families S, T and ST.

testicular atrophy were also excluded as diagnostic criteria. All individuals examined could be classified into one of three groups: normal, myotonia without weakness, and myotonia plus weakness.

Electromyography (*EMG*) was performed on 64 individuals. Three normal relatives examined at their home and 12 patients with obvious clinical myotonia were not examined. A standard electromyograph (Disa) and concentric needle electrodes were used. EMG was performed only in search of myotonia in order to cause as little discomfort as possible. In most patients only the abductor pollicis brevis muscle was examined, in some also the extensor digitorum communis of the forearm. Myotonic discharges were diagnosed if one or more bursts of spontaneous electrical discharges with characteristic waxing and waning of frequency and amplitude were seen or heard.

Slit-lamp examination was performed on all but 5 relatives. Three of these had already been operated upon for cataracts. A standard fixed slit-lamp was used and in 4 cases a high resolution portable slit-lamp (Kowa). Mydriatics were not administered as the examination was performed in a dark room. A diagnosis of myotonic cataract was made if, in the anterior or posterior cortex, fine white dust-like opacities were found interspersed with a sufficient number of iridescent coloured opacities (Junge, 1966). Since no quantitative criteria appear to exist we arbitrarily took a number of ten coloured opacities as a minimum for diagnosis. If white opacities alone were seen, slit-lamp examination was classified as normal. Fleischer's star-shaped polar cataract and mature white or grey cataracts were not accepted as a myotonic cataract, unless coloured opacities were also present; these cases were also classified together with the normals.

Criteria for Diagnosis

Dystrophia myotonica was diagnosed if in addition to myotonia either muscle weakness, myotonic cataracts or both were found and also in S II-1 and ST III-8 (*see* Results). Myotonia congenita was diagnosed if myotonia was found in the absence of muscle weakness and cataracts.

Linkage Study

Blood and saliva samples were taken from all the available potentially informative members of the Families ST and T; only saliva from Family S. Immediately after collection the saliva samples were heated for ten minutes at 100° C in a waterbath in order to prevent deterioration of the H, A, B antigens due to bacterial activity. The secretor status (presence or absence of the ABO antigens in the saliva) was determined by the agglutination-inhibition technique, with anti-H, -A and -B antisera, and detector cells of groups O, A_2 and B (Race and Sanger, 1975).

The blood was typed for the following 26 additional polymorphic systems (for technical details *see* Breuning, van den Berg-Loonen, Bernini, Bijlsma, van Loghem, Meera Khan and Nijenhuis, 1977): the blood group systems ABO, MNS, P, Lutheran (Lu), Rhesus (Rh), Kell (K), Duffy (Fy); the serum protein systems Gm-A_2m and Km (genetic markers of immunoglobulins), α_1-antitrypsin (Pi), transferrin (Tf), C3 complement, group specific component (Gc), haptoglobin (Hp) and pseudocholinesterase (E1 and E2); the red cell enzyme systems red cell acid phosphatase (ACP1), adenosine deaminase (ADA), 6-phosphogluconate dehydrogenase (PGD), phosphoglucomutase-1 (PGM1), red cell adenylate kinase (AK1); glutamic pyruvic transaminase (GPT), NADPH-diaphorase (DIA2), esterase-D (ESD), glyoxalase-1 (GLO1) and superoxide dismutase-1 (SOD1).

Linkage analysis was performed for myotonia congenita in connection with the various marker genes, using Morton's lod score method (Maynard-Smith, Penrose and Smith, 1961). In order to use additional information (namely, the information from families with one or two missing parents and that from the clustering of the separate nuclear families) a method of calculation similar to that employed by Ott's LIPED computer programme was used (Ott, 1974; *see also* Breuning *et al.*, 1977). In this method lod scores were determined separately for three generation clusters, *viz.* the ST family and the posterities of the individuals 1 and 4 in generation I of family T (*see* fig. 1).

RESULTS

In family S, 11 relatives were found to have dystrophia myotonica, 9 were normal and myotonia congenita was not found. In family T, 20 relatives had myotonia congenita, 11 were normal and dystrophia myotonica was not diagnosed. In family ST, 6 relatives were found to have dystrophia myotonica, 12 had myotonia congenita and 11 were normal.

Table 1 summarizes the results classified per method of examination.

TABLE 1. RESULTS IN THE FAMILIES S, T AND ST

			Neurological examination			*Slit-lamp examination*			*Electromyography*		
Family	*Diagnosis*	*Total*	*Normal*	*Myotonia without weakness*	*Myotonia plus weakness*	*Normal*	*Myotonic cataract*	*Not examined*	*Normal*	*Myotonia*	*Not examined*
S	Dystrophia myotonica	11	1	1	9	0	8	3*	0	3	8
	Normal	9	9	0	0	9	0	0	8	0	1
T	Myotonia congenita	20	4	16	0	20	0	0	0	17	3
	Normal	11	11	0	0	11	0	0	9	0	2
ST	Dystrophia myotonica	6	3	0	3	2	4	0	1	5	0
	Myotonia congenita	12	2	10	0	11	0	1	0	11	1
	Normal	11	11	0	0	10	0	1	11	0	0

* Had been operated on for cataracts.

In Family S, 9 of the 11 dystrophia myotonica patients had myotonia plus weakness and all had abnormal lenses (8 had myotonic cataracts, 3 patients had had their cataracts removed). One relative (II-6) was normal on physical examination, but he had myotonic cataracts and electromyographic myotonia. II-1 had percussion myotonia without weakness, but he was still diagnosed as dystrophia myotonica since his cataracts had been removed and his two sons had dystrophia myotonica. All 9 relatives diagnosed as normal in this family were examined by slit-lamp and 8 of these by EMG.

The age of onset and the severity of the symptoms varied much in Family S, as is usual in dystrophia myotonica. Some had only subclinical or mild disease at an advanced age (II-1 and II-6), but most had disabling muscle weakness combined with slowing mental activity (II-13, II-14, III-1, III-3 and III-10). In 2 patients (III-4 and III-5) the disease had started early and the mental retardation was as disabling as the muscle weakness. In all 5 patients from generation III the symptoms were severe enough to prevent them from having normal jobs or attending normal schools.

Fig. 2 represents S III-3 at the age of 41 years. He noticed cramps and weakness of the hands during military service when aged 20 years. The weakness gradually progressed, he had to give up his administrative job and he now works in a sheltered workshop.

At 41 years he appeared slow but of normal intelligence. He had moderate weakness of facial and distal limb muscles, atrophic temporals and sternomastoids and myotonia of grip. Slit-lamp: myotonic cataracts. EMG was not performed.

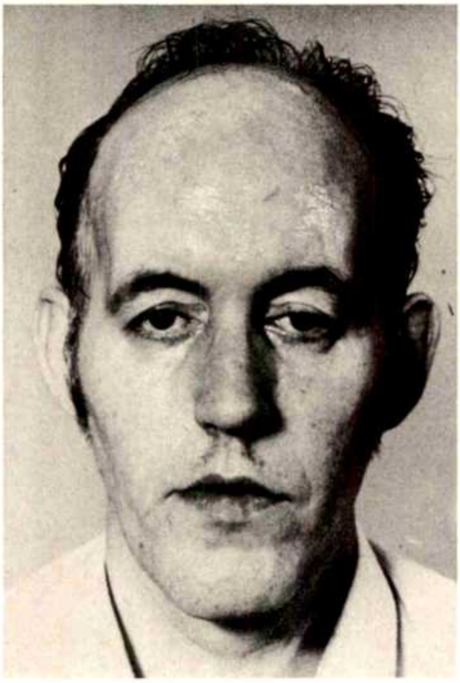

FIG. 2. *Patient S III-3.* Dystrophia myotonica. Wasting of the temporal muscles and weakness of the eyelids and facial muscles.

In Family T, 20 patients had clinical or electromyographic myotonia but neither muscle weakness nor myotonic cataracts were found. Table 1 shows that 4 patients had no active or percussion myotonia but myotonic discharges were seen on the EMG. Eleven relatives were diagnosed as normal, but in 2 of them EMG could not be performed (I-5 and IV-5; these individuals are not included in the linkage study). They may have had subclinical myotonia congenita. All relatives were examined by slit-lamp.

The severity of the myotonia, the frequency of its occurrence and the number of muscle groups involved varied widely. Some patients noticed cramps every day and in most muscles of the body, inhibiting any sudden movement or new activity. In these severe cases, myotonia had always started in early childhood. Others noticed only mild stiffness in a few muscles during some days of the year. In most of these mild cases myotonia was first noticed as late as puberty. EMG usually showed abundant myotonic discharges even when clinical myotonia was mild or absent. II-8 had never noticed cramps and he had no clinical myotonia, but he had profuse electromyographic myotonia when examined at the age of 61 years.

Muscle hypertrophy was present in all patients, it was marked in some, but mild in most cases. In most patients myotonia had increased from childhood to puberty and had been the most severe between the age of 15 and 30 years. In mild cases this was usually the only period in which cramps had been noticed. A remarkable feature in all older patients in Family T was the gradual decline of myotonia after the age of 30. Even in severe cases the sometimes disabling cramps gradually changed into an infrequent and mild inconvenience. This benign course contrasted with the progressive deterioration in the dystrophia myotonica patients in Family S.

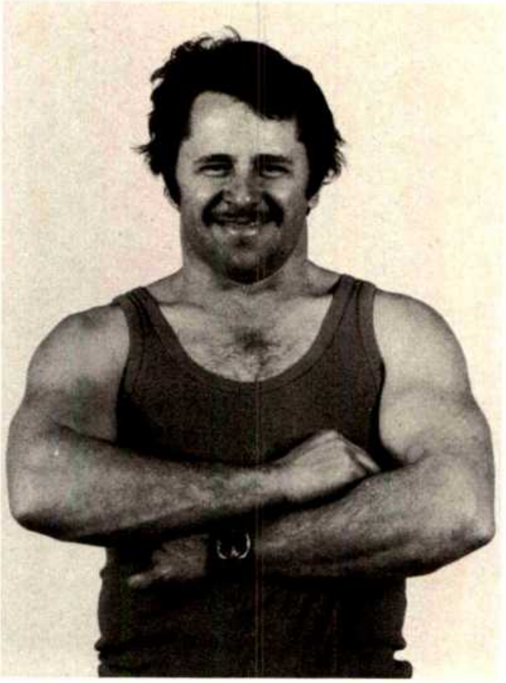

FIG. 3. *Patient T III-8.* Myotonia congenita. He has generalized myotonia of more than thirty years' duration. No weakness of the facial muscles; generalized muscle hypertrophy.

Fig. 3 represents T III-8 at the age of 30 years. Since early childhood he had had cramps in most muscle groups of the body. The cramps were the most severe in damp weather and during emotional tension. They were provoked by sudden movements so that he sometimes could not move for a moment and fell like a log on the ground. He was a fitter and was remarkably well adapted to his cramps so that he could continue working.

Examination showed marked muscle hypertrophy, and myotonia of the eye muscles, eyelids, neck, forearms and hands; muscle weakness was absent. Slit-lamp examination was normal and the EMG showed myotonic discharges.

In Family ST, dystrophia myotonica was found in II-3 and in II-5. They were both asymptomatic but they had myotonic cataracts and electromyographic myotonia. Dystrophia myotonica was also diagnosed in their offspring: III-8 had myotonic cataracts as the only sign and III-13 and III-15 had myotonia with characteristically localized weakness. IV-8 had the congenital form of dystrophia myotonica. He had had breathing and feeding difficulties in the neonatal period and when examined at the age of 10 years, he was slow and had a tent-shaped mouth, nasal speech and weakness, plus myotonia of the hands. The variability of the age of onset and of the severity of the symptoms in these patients was similar to those seen in Family S.

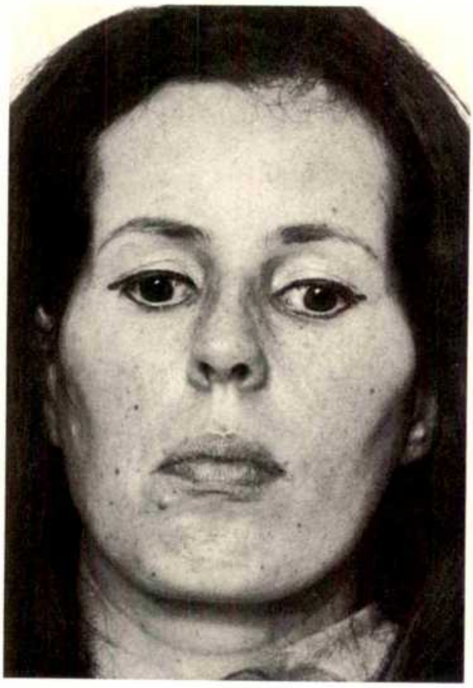

FIG. 4. *Patient ST III-15*. Dystrophia myotonica. Wasting of the temporal and masseter muscles and weakness of the eyelids and facial muscles.

Fig. 4 shows ST III-15 at the age of 30 years. She started to tire quickly and drop things from her hands when aged 25 years. The weakness progressed slowly and she also got cramps in her hands.

When examined at the age of 30 years, she appeared of normal intelligence and held an administrative job. She had a myopathic face, mild weakness of the neck and distal arm muscles and moderate weakness of the distal leg muscles. She had nasal speech and a myotonic grip. Slit-lamp examination showed non-diagnostic white subcapsular opacities. Myotonic discharges were present in the EMG.

Myotonia congenita was found in II-1, II-2, II-4 and in their offspring. Table 1 shows that muscle weakness was not found in any of them and in all slit-lamp examination was normal. The severity, the frequency of occurrence and the distribution of the myotonia in these patients were similar to those in Family T and severe and mild cases seemed to occur at random. After the age of 30 years all these patients showed a gradual decline of myotonia. Again, this favourable course contrasted with the progressive course in the dystrophia myotonica patients in the same family.

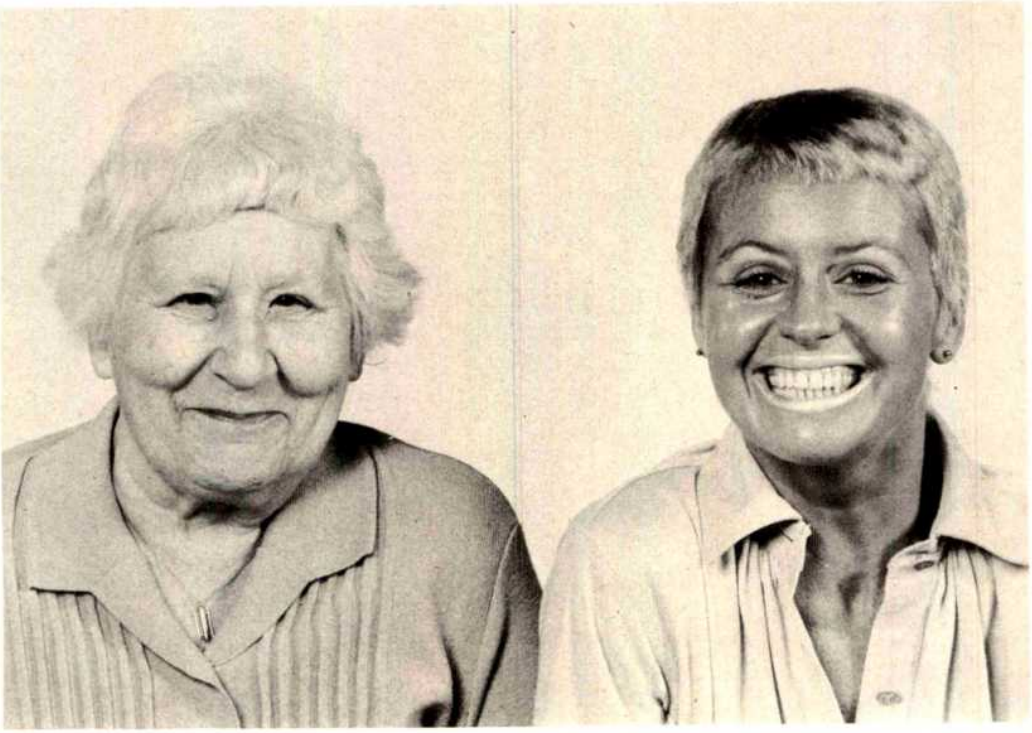

FIG. 5. *Patients ST II-4 and ST III-11.* Myotonia congenita. Generalized myotonia of more than sixty and twenty years' duration. No weakness of the facial muscles.

Fig. 5 shows ST II-4 and her daughter ST III-11. Since early childhood ST II-4 had had generalized cramps including the extraocular muscles. The cramps were more severe and occurred daily during her pregnancies but they diminished after the age of 40 years. When examined aged 68 years she only noticed mild stiffness during a few days a year. Clinical myotonia could not be found, but the EMG showed abundant myotonic discharges. There was no muscle weakness and the slit-lamp examination was normal.

Her daughter, ST III-11, had had myotonia since early childhood. This increased in severity and frequency after puberty and the cramps became painful, leading to a temporary incapacity to work. When examined at the age of 28 years, she had generalized myotonia but no weakness and normal eye-lenses.

In Family ST, 11 first degree relatives were diagnosed as normal. Table 1 shows that in all cases an EMG was performed and 10 were examined by slit-lamp. Altogether they have 20 children who are not represented in the pedigree in fig. 1. Eleven of these were examined and proved normal. The remaining 9 were reported by their parents as not having muscle cramps or weakness.

Relatives having both diseases were not found in Family ST. One may wonder whether a combination of both diseases could have been diagnosed. We assume this would have been possible in most cases, as myotonia congenita always starts in early life, while dystrophia myotonica often starts at a later age. Someone having both diseases would probably have myotonia in childhood, while dystrophic signs could be expected to appear after an interval longer than usual in dystrophia myotonica. Such a patient might also show an intermediate clinical picture, for instance, generalized myotonia and muscle hypertrophy combined with localized muscle atrophy or myotonic cataracts. Such patients, however, were not found in Family ST.

At the time of this study S I-4 and T I-3 had died. According to their children S I-4 had not had muscle weakness or cataracts. She died at the age of 76 years. T I-3 was reported to have suffered from lifelong muscle cramps but not to have had weakness or cataracts and he died at the age of 71 years. Abortions or stillbirths were not reported by their children.

Linkage Studies

The dystrophia myotonica patients ST II-3 and the affected children of S II-1 and of ST II-5 were non-secretors (genotype *se/se*). This indicates that the dystrophia myotonica gene (*Dm*) in the Families S and ST is linked to *se*, which is the silent (recessive) allele at the secretor locus. All other individuals in generation II of the Families S and ST were secretors.

Throughout the pedigree, secretor Dm patients never produced any non-secretor normal offspring with the sole exception of the individual ST III-16, who probably originated from a recombination between the *Dm/dm* and *Se/se* genes in parent ST II-5.

One further direct linkage information is provided by ST III-14, who was unaffected and was found to be a secretor. Her affected father was a heterozygote for secretor (*Se/se*) and her mother was a non-secretor (*se/se*), which indicates that ST III-14 is a non-recombinant.

Family S did not produce further genetic information since in generation II all Dm patients were married to Se partners and all offspring were also secretors (with the exception of S III-1 and -3, already mentioned).

The total direct information for linkage of *Dm* and *Se* in the pedigree amounts to 5 non-recombinants (S III-1, 3; ST III-13, 14, 15) and one recombinant (ST III-16).

The non-recombination status of S II-1 and of ST II-3 and -5 cannot be ascertained, since it is not known whether their Dm parents were secretors (heterozygote *Se/se*) or non-secretors (*se/se*). The observed ratio of 5 non-recombinants and one recombinant is in good agreement with the known recombination frequency of about 10 per cent (expected ratio is 5.4 non-recombinants to 0.6 recombinants).

The results of the linkage analysis with respect to myotonia congenita (Mc) are summarized in Table 2.

TABLE 2. LOD SCORES WITH MYOTONIA CONGENITA

	θ = 0.00	*0.05*	*0.10*	*0.20*	*0.30*	*0.40*
ABO	−∞	−3.957	−2.025	−0.471	+0.095	+0.108
MNS	−∞	−5.272	−3.104	−1.290	−0.537	−0.196
P	−∞	−1.341	−0.899	−0.414	−0.160	−0.038
Rhesus	−∞	−8.813	−5.733	−2.906	−1.476	−0.601
Duffy	−0.835	−0.729	−0.613	−0.375	−0.172	−0.043
Lutheran	−∞	−3.114	−1.833	−0.772	−0.286	−0.064
Secretor	−∞	−1.027	−0.412	+0.041	+0.160	+0.090
Gm	−∞	−3.812	−2.244	−0.935	−0.325	−0.135
Hp	−∞	−3.305	−1.632	−0.321	+0.139	+0.192
C3	−∞	−1.209	−0.719	−0.339	−0.189	−0.092
Pi	−∞	−0.950	−0.536	−0.190	−0.059	−0.011
Gc	−∞	+0.162	+0.498	+0.667	+0.560	+0.311
PGM1	−0.085	−0.008	+0.027	+0.048	+0.054	+0.049
ACP1	−∞	−0.093	+0.298	+0.452	+0.334	+0.142
ESD	−∞	−1.884	−1.077	−0.378	−0.082	+0.025
GPT	−∞	−1.653	−0.882	−0.246	−0.024	+0.015
GLO1	−∞	−5.444	−3.108	−1.282	−0.512	−0.179

Not informative: Kell; Km; Tf; E1; E2; ADA; AK1; PGD; DIA2; SOD1.

Ten of the 27 marker-gene systems investigated were not informative, meaning thereby that no sibships occur in the T or ST families in which both the *Mc/mc* genes and different alleles of these marker genes segregate simultaneously. No firm linkage could be established between the locus determining Mc and any of the other 17 informative marker genes since no lod-score values above +3.0 were observed. Exclusion is demonstrated (lod scores below −2.0) for linkage with 20 per cent recombination or less with *Rh*, for 10 per cent or less with *ABO*, *MNS*, *Gm* and *GLO1*, for 5 per cent or less with *Lu* and *Hp*, and very close linkage with the loci for 8 other marker-gene systems. Slightly positive (but by far not statistically significant) lod scores are observed for *Gc* and *ACP1* (in both the cases at a maximum recombination value of 20 per cent). Since in most cases of true linkage a higher incidence of non-recombinants occurs amongst paternal than amongst maternal segregations (a smaller number of crossing-overs during meiosis in males than in females), lod scores for paternal and maternal segregations have been

TABLE 3. SPECIFICATION OF SOME OF THE LOD SCORES WITH MYOTONIA CONGENITA

		$\theta = 0.00$	0.05	0.10	0.20	0.30	0.40
ACP1	Paternal	$-\infty$	+0.628	+0.742	+0.646	+0.410	+0.160
	Maternal	$-\infty$	−0.721	−0.444	−0.194	−0.176	−0.018
Gc	Paternal	−0.256	+0.119	+0.247	+0.313	+0.254	+0.130
	Maternal	$-\infty$	−0.014	+0.201	+0.318	+0.286	+0.175
Se	Family T	−0.139	+0.125	+0.213	+0.235	+0.175	+0.088
	Family ST	$-\infty$	−1.152	−0.625	−0.194	−0.015	+0.002
Lu	Family T	$-\infty$	−3.114	−1.833	−0.772	−0.286	−0.064
Se	Fam. ST+ Lu Fam. T	$-\infty$	−4.266	−2.458	−0.966	−0.301	−0.062

calculated separately for these two marker genes and shown in Table 3. Especially in the case of *ACP1* the paternal score is much more positive than the maternal lod score, but also in this way the results remain inconclusive. The lod score for *Se*, which becomes slightly positive for higher recombination values, has been composed of the scores of two familial clusters, the offspring of T I-4 and of the ST family. The posterity of T I-1 was not informative. The genetic information concerning *Mc* and *Se* is much more substantial in the ST than in the T I-4 cluster, which contains only one informative individual, T IV-6, being a non-recombinant for *Mc* with *Se* as well as for *Mc-Lu*. Much information for *Lu* is available from the T I-4 cluster; the two other clusters are non-informative.

Since *Se* and *Lu* are linked ($\theta = \sim 0.10$), for the sake of argument the *Se* information of cluster ST may be combined with the *Lu* information of the cluster T I-4, and the poor Se information of family T may be neglected (Table 3); the resultant lod score is found to be more negative. Since the distance between *Dm* and *Se* is about 10 centimorgans and that between *Dm* and *Lu* about 20 centimorgans, it may be more reasonable to combine the *Se* lod score for 10 per cent of recombination in family ST and the *Lu* score for 20 per cent of recombination in Family T. The resulting score, −1.397 is a strong argument against the hypothesis that dystrophia myotonica and myotonia congenita are allelic. A lod score of −1.397 means that the probability of the composition of the pedigree, *viz*. the observed distribution in the various members of the family of the phenotypes of *Mc*, *Se* and *Lu*, is 25 times less probable under this hypothesis than under the alternative hypothesis of genetic independence of *Dm* and *Mc*. We, therefore, concluded that most probably dystrophia myotonica and myotonia congenita are genetically unrelated diseases.

DISCUSSION

This family study shows that in Family S only dystrophia myotonica occurred and in Family T only myotonia congenita. We concluded that, of the deceased ancestors, S I-4 probably had carried the gene for dystrophia myotonica and that

T I-3 probably had had myotonia congenita. Two of their 5 children had dystrophia myotonica and 3 myotonia congenita and both diseases were transmitted independently to the succeeding generations. Intermediate patients were not seen.

Dystrophia myotonica was diagnosed from characteristic signs other than myotonia: muscle weakness and myotonic cataracts. Myotonia congenita was diagnosed on the finding of myotonia in the absence of signs of dystrophia myotonica and one might question if these were not still to come. However, the fact that many patients diagnosed as myotonia congenita had had myotonia for a long period makes this unlikely. This is illustrated in Table 4, which shows the duration of myotonia recorded from history data in the Families ST and T. In generation II myotonia had been present from forty to seventy years, and in generation III between twenty and forty years. This long duration of myotonia rules out a diagnosis of dystrophia myotonica, since in this disease muscle weakness usually starts simultaneously with or only a few years after the onset of myotonia (Thomasen, 1948). In generation IV and V the duration of myotonia was too short to rule out dystrophia myotonica. However, even in these cases we had little doubt about the diagnosis of myotonia congenita, as we did not find facial weakness, nasal speech or mental retardation, which are characteristic of dystrophia myotonica with onset in childhood (Harper, 1975).

TABLE 4. DURATION OF MYOTONIA IN MYOTONIA CONGENITA PATIENTS

Generation	*Family ST*				*Family T*							
II	68	66	63		56	55	61	0*	38	39		
III	40	40	23	20	30	22	14	34	?**	31	26	18
IV	26	2	5	9	7	1	0	7	1	2		
V	1											

Duration of muscle cramps in years in 32 patients of Families ST and T. If cramps started in 'early youth' 5 years was taken as age of onset. * = asymptomatic patient showing myotonia on EMG. ** = no data available in a patient mentally retarded after meningitis in childhood.

In the second generation of Family ST, one might expect an equal number of children with dystrophia myotonica, myotonia congenita, both diseases or no disease. The latter two possibilities did not occur. This may have happened by chance, but the combination of both diseases may also have been incompatible with life.

The chance that in a family with one Dm and one Mc parent all five children will have either the *Dm* or the *Mc* gene, is $0.5^5 = 3.1$ per cent. If the combination of both genes in one individual would be incompatible with life, this chance would be increased to $0.6667^5 = 13.17$ per cent.

Two further, though only theoretical possibilities, could be that either *Mc* is epistatic over *Dm*, or *Dm* over *Mc*. If so, it might be possible that double heterozygotes would belong either to the Mc phenotype (Dm symptoms are suppressed) or to the Dm phenotype (Mc symptoms suppressed by Dm). Such suppositions may sound very unrealistic; nevertheless, in the first case, ST II-1, -2 and -4 would be either single heterozygotes *Mc/mc*, *dm/dm* or double heterozygotes *Mc/mc*, *Dm/dm*; ST II-3 and 5 would be single heterozygotes *mc/mc*, *Dm/dm*. It is, however, improbable that ST II-1 is such a double heterozygote, since in the family *Dm* is linked to *se*, and since she, being a secretor, has one normal, non-secretor, offspring (ST III-4). Also ST II-2 is secretor, and ST III-6 is non-secretor. As a consequence, if ST II-2 were a double heterozygote, also ST III-6 should, most probably, be such a double heterozygote. The chance of five sibs, each of them affected by one disease (generation II) under this hypothesis is, therefore $0.5^3 \times 0.75^2 = 7.0$ per cent instead of 3.1 per cent, thus providing an additional 3.9 per cent of chance. This additional chance is, however, decreased by the fact that ST II-2 has one *dm/dm* daughter (ST III-7) and one *dm/dm* grandson (ST IV-5), whose father is also *Mc/mc*, *Dm/dm*, and that ST II-4 has one *dm/dm* son (ST III-9). If these facts are introduced in the calculation of the probability of sibship ST II, this results into a probability of 4.4 per cent instead of 3.1 per cent, and the initial additional 3.9 per cent of chance has been decreased by only 1.3 per cent. In the same way the probability of sibship ST II would be only slightly increased by the other alternative hypothesis, of epistasis of *Dm* over *Mc*, *viz.* 6.0 per cent instead of 3.1 per cent. There is, therefore, little sense in raising such doubtful suppositions as hypothetical epistasis of one genetical disease over another, only in order to get a higher probability that a sibship may arise in which all sibs are alternatively affected by one disease.

The distinctness of dystrophia myotonica and myotonia congenita was first questioned by Maas and Paterson (1939) when they described patients with a 'transitional form' between the two diseases. Later authors also reported transitional patients (Walton and Nattrass, 1954; Caughey, 1958). One might have expected to find patients with a transitional form in Family ST. However, these were not found, all patients showing a distinct clinical picture of either the one or the other disease.

The transitional forms described in the literature appear to be diverse. Most of them, however, can probably be categorized into one of the following three diagnostic pitfall groups: first, patients presenting with myotonia but later developing dystrophia myotonica (Maas and Paterson, 1939). To diagnose myotonia congenita in such patients is confusing and this diagnosis should only be made if either the patient or a relative had had myotonia without weakness for a long period.

The second group comprises patients having the autosomal recessive type of myotonia congenita which was identified by Becker (1957, 1977). They show the main features of myotonia congenita such as generalized severe myotonia and muscle hypertrophy, and in addition they often have mild atrophy and weakness of the distal arm and neck muscles. However, in this disorder myotonic cataracts have not been described and the recessive inheritance further marks the distinction.

The third group comprises patients with myotonia and non-specific 'dystrophic' signs. For example, Caughey (1958) described three patients in one family with lifelong myotonia and muscle hypertrophy; he diagnosed dystrophia myotonica because they all had early balding and two also had non-specific cataracts and some wasting and weakness of neck flexors and abdominal muscles. In our opinion stricter criteria are necessary for distinguishing dystrophia myotonica from myotonia congenita, and non-specific cataracts, frontal balding or mental retardation (Caughey, 1979) should not be used for this purpose. Moreover, mild atrophy and weakness of neck flexors are also rare but well documented signs in dominant myotonia congenita (Becker, 1977); they are probably caused by longstanding and severe myotonia, in a similar way as the mild muscle wasting often seen in recessive myotonia congenita. They differ from the muscle atrophy of dystrophia myotonica in being much milder, occurring later and showing little progression. However, these patients may be very difficult to distinguish individually from patients with dystrophia myotonica. Sometimes family studies will have to be performed in search of unequivocal signs in relatives, such as myotonic cataracts or lifelong myotonia without weakness.

This family study confirms the view of previous authors (Bell and Martin, 1947; Thomasen, 1948; Klein, 1958; Harper, 1979) that dystrophia myotonica and myotonia congenita show a clearly distinct clinical picture. The fact that both diseases could easily be distinguished clinically even in Family ST, and that they were transmitted independently in this family provides new evidence that they are caused by two distinct genetic defects.

This conclusion is largely confirmed by the results of the linkage analysis, since the well established linkage of *Dm* with the marker genes *Se* and *Lu* does not find its reflection in linkage between *Mc* and *Se* and *Lu*. On the contrary such a linkage appears to be very unlikely, and this means that *Dm* and *Mc* are separate genes, localized in different parts of the genome.

SUMMARY

In a unique sibship of 5, 2 siblings were found to have dystrophia myotonica and 3 had myotonia congenita. A study was made of the paternal and maternal families and of the offspring of the 5 siblings. Eighty relatives were examined clinically, by slit-lamp and by electromyography.

In the relatives of the mother of the sibship only dystrophia myotonica was found and in the relatives of the father only myotonia congenita. In the offspring of the sibship the two diseases were transmitted independently in the successive generations.

All patients showed a clinical picture of either one or the other disease and transitional clinical forms were not found.

A linkage study was performed in the family with myotonia congenita and in the family in which both diseases occurred. The myotonia congenita gene is probably not linked to the secretor and lutheran genes. The hypothesis that there is no linkage between myotonia congenita and the secretor-lutheran linkage group was found to be 25 times more probable than the alternative hypothesis that myotonia congenita is linked to this group.

This family study therefore provides evidence that dystrophia myotonica and myotonia congenita are both clinically as well as genetically distinct.

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Dr Höweler's present address: Limburg University, Department of Neurology, P.O. Box 616, Maastricht, The Netherlands.

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NATURE OF THE REVERSIBLE WHITE MATTER LESION IN MULTIPLE SCLEROSIS

EFFECTS OF ACUTE INFLAMMATION ON MYELINATED TISSUE STUDIED IN THE RABBIT EYE

by M. DALAKAS[1], R. G. WRIGHT *and* J. W. PRINEAS

(*From The Neurology Service, Veterans Administration Medical Center, East Orange, New Jersey, and the Department of Neurosciences, College of Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, New Jersey, USA*)

INTRODUCTION

THE acute symptoms that accompany the appearance of a fresh lesion in the central nervous system in multiple sclerosis often improve rapidly and disappear completely over the course of a few weeks. While studies of visually evoked responses in patients with acute optic neuritis indicate that such symptoms are the result of a complete conduction block rather than slowing or other disturbances in conduction (Halliday, McDonald and Mushin, 1973; Halliday and McDonald, 1977), it remains uncertain whether or not this reversible dysfunction affects chiefly myelinated nerve fibres or demyelinated nerve fibres (McDonald, 1975).

Most recent authors have been inclined to accept myelin loss *per se* as the morphological basis of the conduction block, with recovery dependent upon the establishment of conduction in *demyelinated* axons (Rogart and Ritchie, 1977; Rasminsky, 1978; Waxman, 1978). The alternative possibility, that remitting symptoms in multiple sclerosis are due to a reversible conduction block in *myelinated* nerve fibres close to the lesion, is suggested by the fact that symptoms frequently reach their maximum intensity within minutes (McAlpine, 1972) which is too rapid to be accounted for by a demyelinative process that depends on macrophage activity, as seems to be the case in multiple sclerosis (Prineas, 1975; Prineas and Connell, 1978). Also Halliday and McDonald (1977) point out that recovery of visual function in optic neuritis coincides with a marked reduction in disc swelling, and they suggest that transient loss of function may be related more to œdema and swelling of the nerve than to demyelination.

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[1] Present address: Medical Neurology Branch, National Institutes of Health, Bethesda, MD 20205, USA.

The present study was carried out to determine whether or not reversible structural changes which might disturb conduction occur in myelinated tissue adjacent to a focus of mild inflammation. An acute inflammatory response was induced in the vitreous of the rabbit's eye, and the bundles of myelinated nerve fibres which run for several millimetres across the surface of the retina in this species (Wray, Cogan and Arnason, 1976; Wiśniewski and Bloom, 1975) were examined for reversible structural changes. The particular inflammatory response selected for study was a *mild* Arthus reaction provoked in measles-sensitized animals by intravitreous injection of the sensitizing antigen. The Arthus reaction was chosen because it is a classical humoral mechanism causing acute reversible inflammation. By selecting measles virus as the test antigen, the study also provided an opportunity to determine whether or not the introduction of measles antigens into the central nervous system of an immune recipient caused local primary demyelination as an incidental, non-specific effect of antigen-antibody interaction analogous to demyelination described in association with delayed hypersensitivity reactions (Wiśniewski and Bloom, 1975; Raine, 1976).

The study revealed that a mild Arthus reaction provoked in the central nervous system by local challenge with measles antigens produces vasogenic œdema together with a striking, selective destruction of astrocytes but no demyelination.

MATERIALS AND METHODS

Twenty-eight adult New Zealand albino rabbits of both sexes were studied. Eight were sensitized to measles, skin tested to determine the degree of hypersensitivity, then challenged by intravitreous injection of the same volume of measles vaccine or normal saline. Some of the remainder served as normal controls, others were used to determine the effects on the retina of intravitreous injection of the same volume of measles vaccine or saline, and the rest were used to study the effects on the retina of measles immunization alone. Animals were immunized using a lyophilized measles virus vaccine prepared from chick embryo cell cultures infected with an attenuated line of Edmonston virus (Attenuvax vaccine supplied by Merck, Sharp and Dohme). The vaccine, dissolved in saline without added antibiotics, was mixed with an equal volume of complete Freund's adjuvant (CFA (Difco)), and 0.1 ml of this mixture was injected into each foot pad under ether anæsthesia. Substituting incomplete Freund's adjuvant (Difco) for CFA, the animals were revaccinated sixteen and twenty-three days later. Skin tests were carried out seventy-two hours after the last immunizing injection, each animal receiving 0.1 ml of the diluted vaccine intradermally in the shaved flank. The 1 : 10, 1 : 100 and 1 : 1000 dilutions of the vaccine produced local erythematous areas, 2 to 10 mm in diameter within six hours in all animals, the 1 : 10 dilution also causing induration in two animals. With these dilutions the skin lesions disappeared within three days. Testing with the 1 : 1 dilution of the vaccine produced necrotic, hæmorrhagic lesions whereas testing with the 1 : 10^4 dilution of the vaccine produced no response.

Intravitreous challenge with the antigen was carried out during the following week, each animal receiving 0.05 ml of the diluted vaccine or the same volume of normal saline in each eye. The injections were given under ether anæsthesia using a 27-gauge needle introduced through the sclera to a point in the vitreous close to the optic disc.

Animals were perfused under ether anæsthesia five hours, three days and six days following eye injection. They were perfused through the left ventricle with 4 per cent paraformaldehyde followed by

5 per cent glutaraldehyde. Blocks were obtained from the optic disc, from the myelinated nerve fibre bundles on the surface of the retina 1, 2 and 3 mm from each side of the optic disc, and from the optic nerve behind the globe. The tissue was postfixed in Dalton's solution and embedded in Spurr's medium for light and electron microscopy. Serum hæmagglutination inhibition measles antibody titres, at the time of perfusion, were determined by Dr S. Houff, Infectious Diseases Branch, National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Maryland.

RESULTS

Measles vaccination appeared not to affect the animals' general health. The intraocular pressure was not increased and no evidence of glaucoma was noticed. The immunized animals developed antibodies against measles with hæmagglutination inhibition titres ranging from 8 to 32.

Intravitreous injections of the vaccine diluted 1 : 1, 1 : 10 and 1 : 100, but not 1 : 1000 caused conjunctival and ciliary injection together with conjunctival œdema which remained prominent for three days and which disappeared or improved by the sixth day. Fundoscopy revealed a cloudy vitreous with precipitates present in the anterior chamber within twenty-four hours of the injection with all concentrations of the vaccine. These signs also improved or disappeared by the sixth day.

Light microscopy revealed that intravitreous challenge with 1 : 1 concentration of the vaccine produced a typical Arthus reaction on the surface of the retina consisting of hæmorrhage, a polymorphonuclear leukocyte exudate, and occlusion of vessels by thrombi. The underlying myelinated tissue revealed extensive axonal degeneration. No evidence of primary demyelination was observed by light or electron microscopy in the remaining nerve fibres, including those adjacent to infiltrating macrophages.

In contrast to the picture just described, the major change observed light microscopically following challenge with lesser concentrations of the vaccine (1 : 10, 1 : 100 and 1 : 1000) was the appearance of vacuoles and clefts in the tissue, together with some loosening (œdema) of the tissue close to the vitreous. This was most marked up to three days following the injection and it largely disappeared over the next three days (fig. 1). Myelinated nerve fibres and oligodendrocytes retained their normal appearance throughout this period, but astrocytes appeared enlarged and watery (fig. 2). The inflammatory cells present three days after challenge were mostly macrophages together with a few lymphocytes and rare plasma cells. At six days plasma cells predominated. Mild reactive gliosis leading to sheathing of superficial retinal vessels by fibrous astroglial processes was evident at six days. Similar changes were absent following intravitreous injections of saline in immune animals and of the vaccine in non-immune animals.

Electron microscopy revealed that the vacuoles were often bound by a unit membrane and that they contained bundles of astroglial filaments, glycogen granules and mitochondria, indicating that they were grossly distended or ruptured astroglial processes (fig. 3). Neighbouring astroglial cell bodies also appeared watery and enlarged as did astroglial processes contacting nodes of Ranvier (fig. 4).

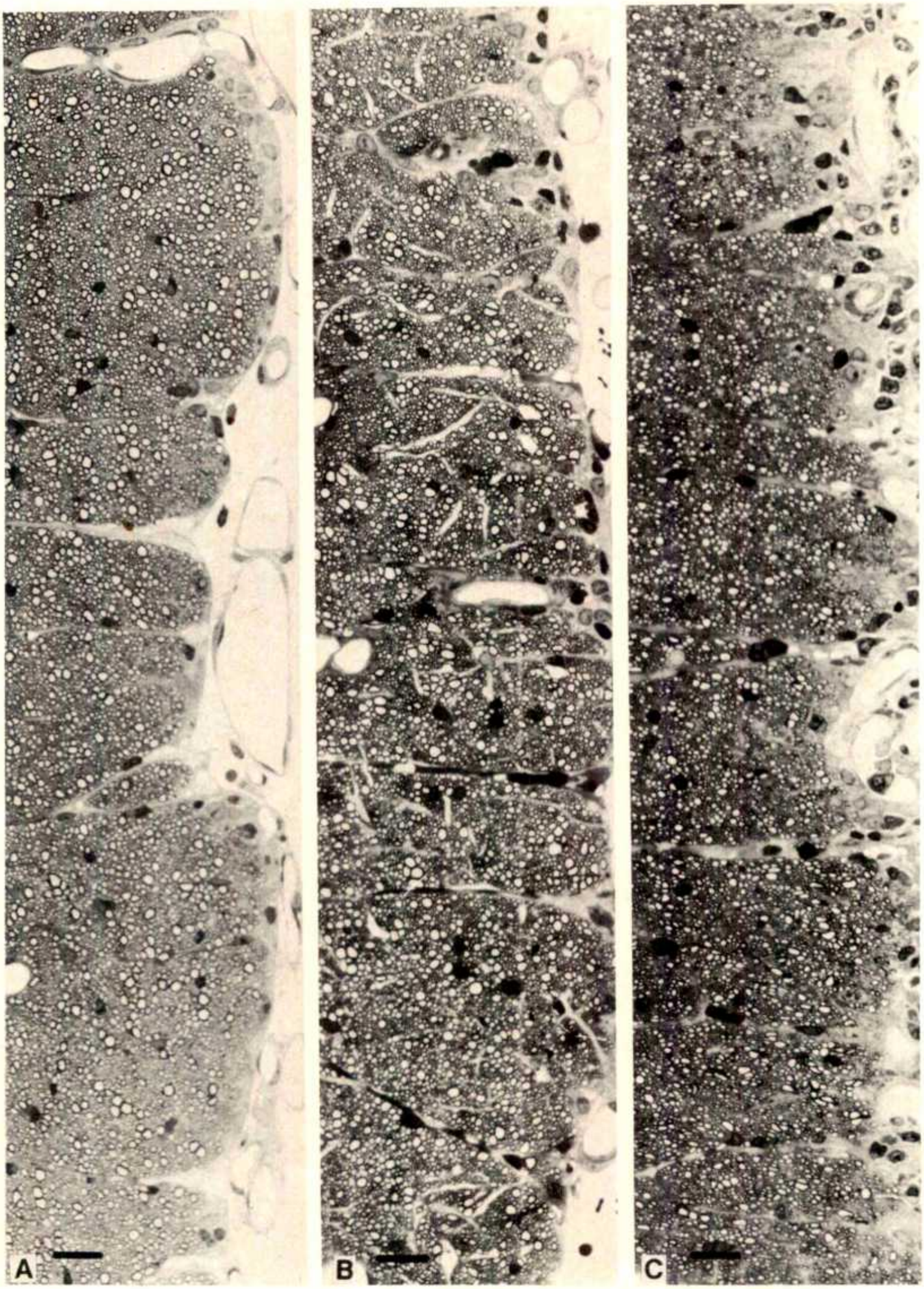

FIG. 1. Changes produced in myelinated tissue on the surface of the rabbit retina by an injection into the vitreous of 0.05 ml of measles vaccine diluted 1:10 in a measles-sensitized animal: A, before injection—tissue appears normal; B, three days after injection—distended astrocytic processes are present throughout the tissue; C, six days after injection—the tissue has returned to normal except for the presence of inflammatory cells, most of which are plasma cells. 1 μm epoxy sections stained with toluidine blue. Bar = 20 μm.

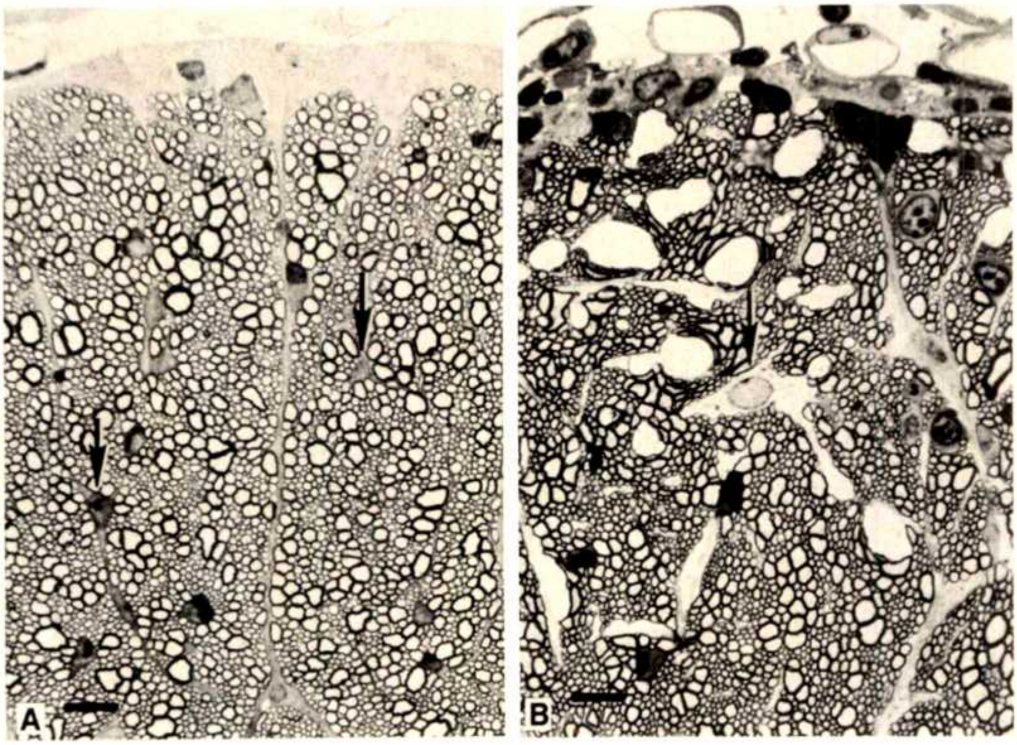

FIG. 2. A, astrocytes (arrows) in myelinated retinal tissue in a normal rabbit appear compact; B, the same tissue three days after the induction of a mild Arthus reaction in the vitreous reveals vacuoles, astrocytic swelling (arrow) and infiltrating inflammatory cells. Nerve fibres appear normal. 1 μm epoxy sections stained with toluidine blue. Bars = 10 μm.

Similar nodal changes, due to imperfect fixation, were observed in control tissue but were much less frequent. There may also have been a mild accumulation of fluid in the intramyelinic extracellular space in nearby myelinated fibres but as this was also a common finding in control tissue, the significance of this is uncertain. There was no evidence that this (equivocal) intramyelinic accumulation of fluid was associated with disruption of terminal loop–axolemmal junctions, of tight junctions at the inner and outer loops, or of tight junctions between adjacent lateral loops at nodes of Ranvier. Electron microscopy confirmed the absence of primary demyelination throughout the course of the experiment, including tissue heavily infiltrated with plasma cells (fig. 5).

DISCUSSION

The Arthus reaction is a hypersensitivity reaction which occurs when an antigen is injected into any vascular organ in a sensitized individual, the resulting interaction of antigen, antibody, complement and polymorphonuclear leukocytes causing vascular damage, leakage of plasma proteins and red cells, and intravascular thrombosis. As the lesion heals, polymorphs are replaced by mononuclear cells, and plasma cells appear (Cochrane 1968; Waksman, 1970). In the present experiment, the findings were typical except that the course was somewhat protracted. This has been noted previously in studies of the Arthus reaction in the rabbit eye and it has been ascribed to retention of immune complexes in the vitreous (Levine and Ward, 1970).

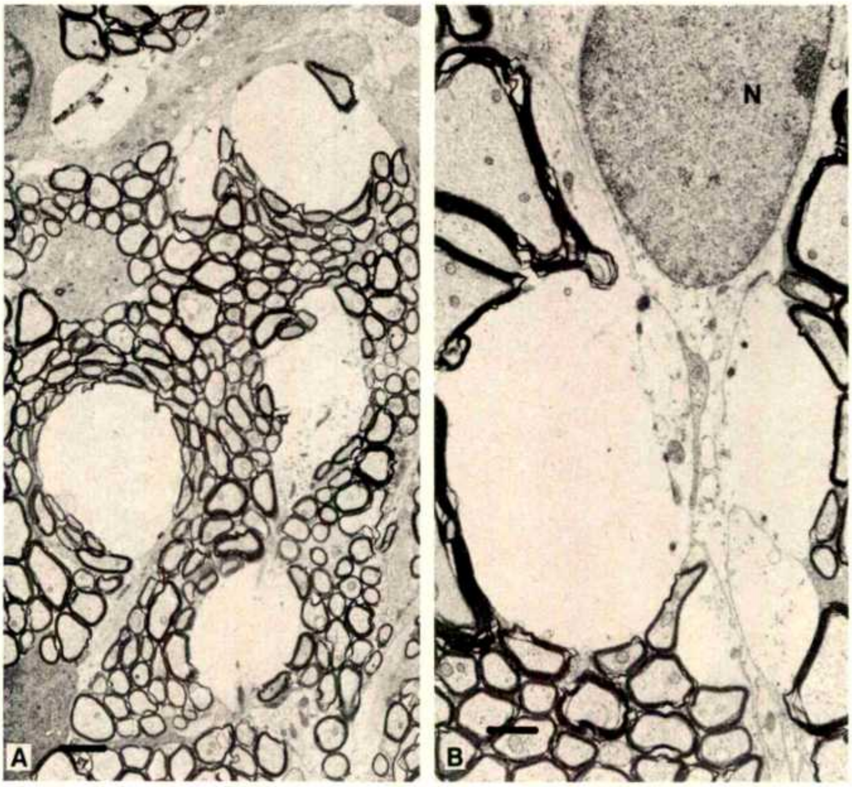

FIG. 3. Electron micrographs of vacuoles present in myelinated nerve fibre bundles on surface of rabbit retina three days after induction of a mild Arthus reaction in vitreous: A, myelinated nerve fibres are displaced and compressed by vacuoles but appear normal otherwise. Bar = 2 μm. B, vacuoles close to a watery astrocyte (N = nucleus of astrocyte). Bar = 0.5 μm.

In previous studies in which antigens such as egg albumin and horse serum have been injected into the central nervous system of sensitized animals, it has been noted that severe Arthus reactions cause local tissue necrosis affecting all components of nervous tissue (Alexander and Campbell, 1937; Jervis, Ferraro, Kopeloff and Kopeloff, 1941; Good, 1950; Roizin and Kolb, 1959). In the present study, it was found that challenge with very small doses of the sensitizing antigen produces a reversible white matter lesion consisting chiefly of astrocyte swelling and rupture together with extracellular and possibly intramyelinic œdema. The absence of primary demyelination in both mild and severe forms of the Arthus response in the present study contrasts with the demyelination seen around foci of chronic inflammation in peripheral nerves (Lehmann and Ule, 1964) and in the vicinity of local delayed hypersensitivity reactions in the central nervous system (Wiśniewski and Bloom, 1975; Raine, 1976) suggesting different responses of the white matter to humoral antigen-antibody interactions and delayed hypersensitivity reactions.

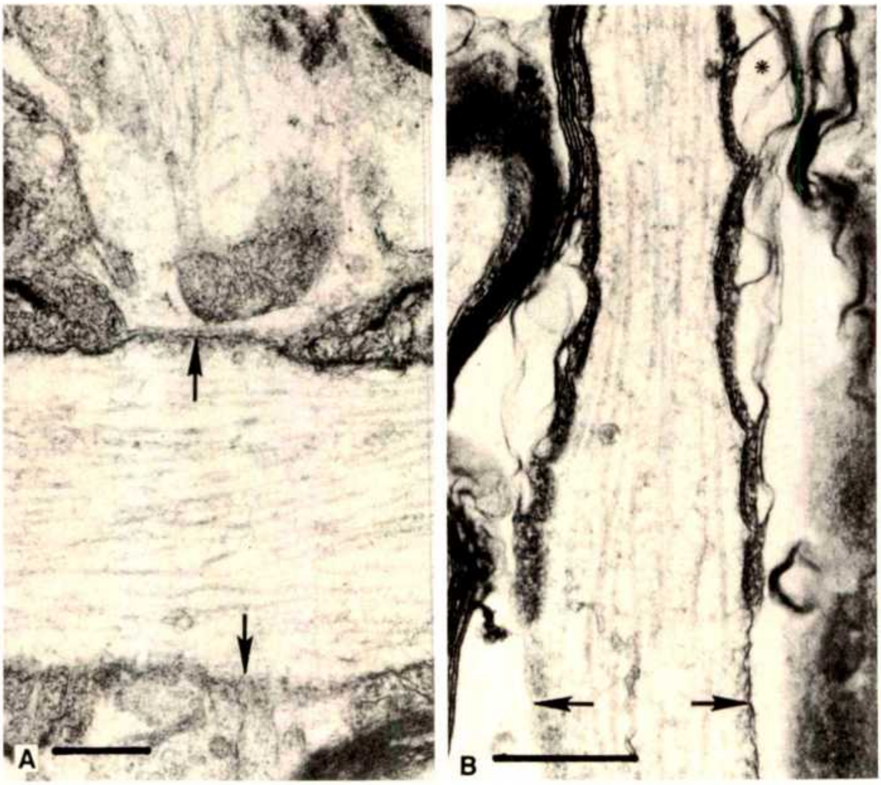

FIG. 4. Electron micrographs of nodes of Ranvier in œdematous myelinated tissue on the surface of rabbit retina three days after the induction of a mild Arthus reaction in the vitreous; A, astrocyte processes can be seen close to the axon membrane (arrows); B, the nodal axon membrane (arrows) is bare and fluid (*) has accumulated between the myelin lamellæ. Bars = 0.5 μm.

The most likely cause of the astrocyte damage observed in the present study would seem to be vasogenic œdema, that is, œdema secondary to a leak of plasma proteins into the tissue from normally impermeable blood vessels. While it is known that under such circumstances astrocytes swell and may rupture, the cause of this is not understood although it has been shown that these cells take up the extravasated protein (Klatzo, 1967; Feigin, 1968; Manz, 1974).

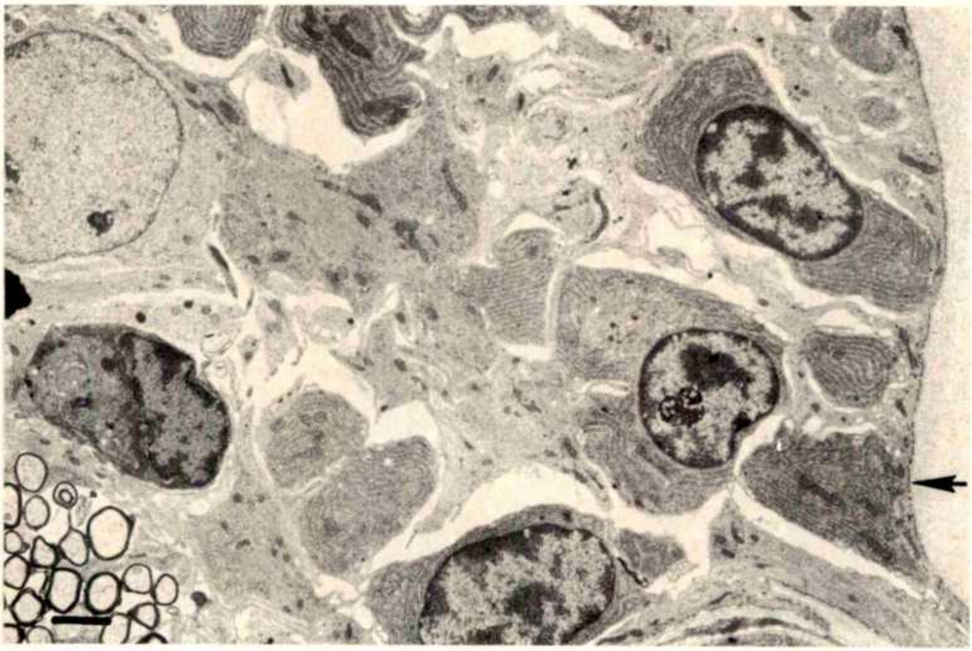

FIG. 5. Electron micrograph of myelinated tissue on the surface of the rabbit retina six days after the induction of a mild Arthus reaction in the vitreous. Plasma cells and other mononuclear inflammatory cells lie under the glial limiting membrane (arrow) close to normal myelinated nerve fibres. Bar = 2 μm.

Of the various reversible structural changes that were observed in inflammed white matter in the present study and which might, theoretically, interfere with nerve conduction, the astrocytic lesion is the most interesting. There is evidence that these cells are important in regulating ion concentrations and possibly ion flow in the extracellular space (Kuffler and Nicholls, 1966). Also it has been observed that astrocyte processes encircle nodes of Ranvier and extend tufts of microvilli-like and foot-like processes through the nodal gap substance to the immediate vicinity of the nodal axonal membrane. It has been suggested that the nodal gap substance in the central nervous system, which may act as an ionic sink as proposed for the gap substance at peripheral nodes (Langley, 1969), may be produced and maintained by these nodal astrocyte processes (Hildebrand, 1971). Attention has also been drawn to the fact that central nodes of Ranvier, in contrast to those in the peripheral nervous system, lack juxtanodal accumulations of mitochondria, suggesting that the special energy demands of nodes in the central nervous system may be supplied by astrocytes (Hildebrand, 1971). The present findings are also in keeping with the view, recently emphasized by Bauer (1978), that corticosteroids speed remissions in multiple sclerosis by reducing œdema.

SUMMARY

Arthus reactions of different intensities were induced in the rabbit eye using measles vaccine as the immunogen. In the presence of a mild Arthus reaction in the vitreous, myelinated nerve fibre bundles on the retinal surface revealed extracellular œdema together with marked swelling and rupture of astrocyte processes, including those bearing a special relationship to nodes of Ranvier. These changes improved or disappeared over the course of six days. No demyelination occurred. The findings implicate an astrocytic lesion as a possible cause of reversible neurological deficit and conduction block associated with acute inflammation in central white matter.

ACKNOWLEDGEMENTS

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THE DUALITY OF THE CINGULATE GYRUS IN MONKEY

NEUROANATOMICAL STUDY AND FUNCTIONAL HYPOTHESIS

by CHRISTINE BALEYDIER *and* FRANÇOIS MAUGUIERE[1]

(From the Laboratoire de Neuropsychologie Expérimentale INSERM U 94, 16, Avenue Doyen Lépine, 69500 Bron, France)

INTRODUCTION

SINCE the study by Papez (1937) of the hippocampo-mamillo-thalamo-cortical pathway, it has been largely accepted that the cingulate gyrus, which is part of MacLean's 'visceral brain' (1949, 1952), is responsible for the emotional colouring of sensations, including pain, and for the motor expression of emotions. Tameness, loss of fear of man and of social sense are the most obvious changes which have been transiently observed in the behaviour of monkeys after bilateral anterior cingulectomy (Smith, 1944; Ward, 1948; Glees, Cole, Whitty and Cairns, 1950; Kennard, 1955; Pechtel, MacAvoy, Levitt, Kling and Masserman, 1958). However, no clear-cut deficits in social behaviour of monkeys were reported by Myers (1975) after bilateral and complete ablation of the cingulate gyri, and Pribram and Fulton (1954) showed that the only effect of bilateral anterior cingulectomy in monkeys is a shortening of the avoidance reaction. Moreover, McCleary (1961) demonstrated in cats that the active avoidance reaction is to be dissociated from the emotional arousal since only the former is abolished after bilateral lesions of the middle half of the cingulate gyrus. In man, bilateral anterior cingulectomies have been performed for the surgical management of psychoses, obsessive neuroses and of intractable pains (Whitty, Duffield, Tow and Cairns, 1952; Le Beau, 1954; Whitty, 1955; Foltz and White, 1962; Ballantine, Cassidy, Flanagan and Marino, 1967; Meyer, MacElhaney, Martin and MacGraw, 1973; Ortiz, 1973; Wilson and Chang, 1974). Although the extent of the lesions largely differs in these studies, all authors agree that bilateral lesions of the anterior cingulate gyrus and/or of the anterior cingulum lower the emotional reactions to the environment or to painful stimuli. The study of Livingston (1953) comparing the effects of bilateral cingulotomy with those of sham operations clearly demonstrates that this benefit is more than a placebo effect.

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[1] EEG Department, Neurological Hospital, 69500 Bron, France.

Electrical stimulation of the anterior cingulate gyrus is known to produce autonomic effects similar to the spontaneous vegetative correlates of emotion, that is, changes in blood pressure and heart rate, respiratory arrest, dilatation of the pupils and pilo-erection. Such effects have been observed in monkeys (Smith, 1945; Ward, 1948; Kaada, Pribram and Epstein, 1949; Showers, 1959; Dunsmore and Lennox, 1950) and in man (Pool and Ransohoff, 1949; Escobedo, Fernandez-Guardiola and Solis, 1973). More complex responses such as fear, anxiety or pleasure have been reported in man after electrical stimulation of the cingulum (Meyer *et al.*, 1973) or of the anterior cingulate area 24 (Talairach, Bancaud, Geier, Bordas-Ferrer, Bonis, Szikla and Rusu, 1973; Bancaud, Talairach, Geier, Bonis, Trottier and Manrique, 1976); these responses, although inconstant, lend substance to the hypothesis of a specific role of the cingulate gyrus in affective behaviour.

The cingulate gyrus is also currently thought to be involved in memory processing. Delay and Brion (1969) and Lhermitte and Signoret (1976) consider that tumoural or vascular lesions of both cingulate gyri can result in anterograde amnesia in man. However, bilateral cingulectomy (or cingulotomy) in man does not cause durable loss of memory (Tow and Whitty, 1953; Meyer, *et al.*, 1973; Teuber, Corkin and Twitchell, 1976; Long, Pueschel and Hunter, 1978). After this operation only a transient confusional state, which contains some elements of Korsakoff's confabulatory syndrome, may be observed for a few days (Le Beau, 1954; Whitty and Lewin, 1957, 1960). In monkeys no major negative effects on memory processing have been demonstrated after bilateral anterior cingulectomy (Pechtel *et al.*, 1958; Pribram and Fulton, 1954; Pribram, Wilson and Conners, 1962). Two explanations may be suggested to by-pass the discrepancy between the effects of spontaneous lesions and of those surgical cingulate ablations on memory. First, one could emphasize that the damage of the inner aspect of the frontal lobes, which is constantly observed in patients with vascular or tumoural bicingulate lesions is, totally or partially, responsible for the memory troubles. The second alternative would be that the bilateral surgical ablations of the cingulate gyrus are too small to induce a memory loss, because they may spare the upper fringe of the gyrus which, in monkeys, contains neurons known to modify their activity during delayed response test (Fuster, 1973; Niki and Watanabe, 1976*a*, *b*).

The third function attributed to the cingulate gyrus is the control of the mechanisms underlying exploratory behaviour and attention toward sensory stimuli. A reduction of spontaneous speech and movements and a depressed reactivity to sensory stimulations and pain are usually observed in man after bilateral ischæmic lesions confined to the territory of the anterior cerebral arteries, which includes the cingulate gyri (Critchley, 1930; Nielsen and Jacobs, 1951; Barris and Schuman, 1953; Ogaya, Fukiyama and Iwaya, 1966; Skultety, 1968; Faris, 1969; Freemon, 1971; Buge, Escourolles, Rancurel and Poisson, 1975). This syndrome differs from the akinetic mutisms due to midbrain and thalamic lesions (Cairns, 1952) and co-exists with a preservation of alertness (Segarra, 1970). Comparable behavioural changes have been reported after bilateral anterior cingulectomy in cats (Kennard, 1955), and in monkeys (Smith, 1944). As for the memory troubles differences in the size of the lesions may account for the absence of long-term impairment of exploratory behaviour or of attention reported by numerous investigators after bilateral surgical cingulectomies in monkey (Ward, 1948; Glees *et al.*, 1950; Pechtel *et al.*, 1958; Showers, 1959) and in man (Tow and Whitty, 1953; Teuber *et al.*, 1976). Moreover a lateralized neglect phenomenon towards contralaterally applied uni- or pluri-modal sensory stimuli has been reported following either unilateral frontal lesions in man (Heilman and Valenstein, 1972) or unilateral ablations of the anterior cingulate cortex in monkey (Watson, Heilman, Cauthen and King, 1973); Heilman and Valenstein (1979) propose that this behaviour of 'hemi-inattention', which is very close to what Welch and Stuteville (1958) have described after lateral frontal lesions in monkeys, could depend on lateralized impairment of exploratory movements, and would be better described as a 'hemispatial hypokinesia'. This view is partly supported by Talairach *et al.* (1973) and Bancaud *et al.* (1976) who observed, during unilateral stimulations of the anterior cingulate gyrus in awake patients, a reaction of arousal associated with mainly contralateral complex movements of the face and of the upper limb which can be modified by external stimuli and are carried out by the subject in a compulsive way.

Thus, in spite of some conflicting data from clinical and experimental studies, one may hypothesize that the cingulate gyrus probably has a functional duality and belongs to both the 'visceral' and the 'intellectual' brain. Emotional colouring of sensations and memory processes could be grouped together; they have obvious psychological links, they are both poorly lateralized within the brain; they both imply anatomical connections with the so-called 'limbic system'. The control of mechanisms underlying attention to sensory stimuli, which could be considered as the second possible function of the cingulate gyrus, is lateralized, and supposes the existence of anatomical connections between the cingulate gyrus and areas of the brain implied in goal-orientated behaviour. One can assume, as proposed by Mesulam and Geschwind (1978) that one of the fundamental roles of attention is to direct vigilance towards events which are of emotional or motivational significance to the organism. Thus, according to the views of Powell and Hines (1974) on the functions of the limbic system, the cingulate gyrus could be considered as an 'interface' between attention and emotion.

Anatomically the cingulate gyrus is heterogeneous and mainly composed of two different cytoarchitectonic areas numbered 24 and 23 on Brodmann's map (1909). The former belongs to the agranular frontal cortex and the latter shows the granular type of lamination. One does not know to which extent the anatomical heterogeneity parallels the functional duality. Several hypotheses can be proposed; the first, suggested by the pioneer work of McCleary (1961) in cats, assumes that areas 23 and 24 could each have their own functions and their own anatomical connections, in which case there remains the question of how functions could be shared between the two areas. Another alternative would be that only one of these two areas is necessary to account for all the functions which have been ascribed to the cingulate gyrus. A third hypothesis could be that the two cytoarchitectonic areas are functionally and anatomically coupled, in the same way as the post-central sensory areas are with the precentral motor cortex (Jones and Powell, 1970; Powell, 1973).

The aim of this paper is to describe the connections of areas 24 and 23 in the monkey, in order to know whether anatomical data lend substance to one of these hypotheses.

MATERIAL AND METHODS

Thirteen adult monkeys were used in this series of experiments. The brains of 2 were processed for autoradiography and 11 for HRP (horseradish peroxidase) technique. The substances injected, areas injected and the species of the animals are listed in Table 1.

TABLE 1

Experiment	*Substance injected*	*Area injected*	*Animal*
1	Proline + leucine	23	Macaca irus
2	Proline + leucine	24	Macaca mulatta
3	HRP	23	Macaca mulatta
4	HRP	24	Macaca mulatta
5	HRP	24	Erythrocebus patas
6	HRP	7	Erythrocebus patas
7	HRP	7	Macaca irus
8	HRP	7	Macaca irus
9	HRP	22	Erythrocebus patas
10	HRP	21	Erythrocebus patas
11	HRP	Superior temporal sulcus (STS). Post-ventral bank	Erythrocebus patas
12	HRP	(STS) Dorsal bank	Erythrocebus patas
13	HRP	(STS) Anterior dorsal bank	Macaca mulatta

The surgical procedure exposed the cortical areas to be injected. To reach the cingulate gyrus, a paramedian incision of the dura was performed. Then by retracting one hemisphere away from the falx, the cingulate cortex was exposed. The location of the splenium and of the genu of the corpus callosum were used as indicators of the level of area 23 and 24 respectively. For injection in the superior temporal sulcus (STS), both banks of the sulcus were separated by dissecting the pia; to inject parietal and temporal lobes, the cortex was simply exposed by opening the dura.

In the case of the autoradiographic experiments, the animals were given two local injections of an amino acid mixture (from New England Nuclear, Proline, L-(2,3-^{3}H), specific activity 20 Ci/mmol, Leucine L-(4,5-^{3}H(N), specific activity 60 Ci/mmol). After evaporation of the original solutions, the labelled material was dissolved in saline to a concentration of 200 μCi/μl. In each experiment two closely spaced injections of 1 μl each were made through a syringe needle (Hamilton syringe, 5 μl gauge) over a period of 30 min. After a survival time of 36 h, the animals were perfused through the heart with a 4 per cent paraformaldehyde solution preceded by a pre-rinse of saline plus procaine. After post-fixation, the brains were embedded in paraffin and cut into frontal sections of 7 μm thickness. The sections are mounted on gelatinized slides and dipped in Ilford K5 emulsion diluted 1:1 in water. Following an exposure time of 4 to 8 weeks, the slides were developed and counterstained with cresyl violet.

HRP (Boehringer grade I or Serva) was delivered into the cortex by 5 or 6 tangential and subpial penetrations with the needle of a Hamilton syringe (5 μl gauge); this procedure allowed a very superficial and strictly cortical injection, without any damage to the underlying white matter. After a survival time of 48 h, the animals were killed by intracardiac perfusion; the brains were freeze-sectioned and the sections were incubated according to the procedure recommended by Lavail and Lavail (1972). A one-in-two series was counterstained with cresyl violet.

All sections were observed under dark-field and light-field illumination. The atlases of Olszewski (1952) and of Shantha, Manocha and Bourne (1968) were used for identification of neuronal structures.

RESULTS

I. POSTERIOR CINGULATE CORTEX (AREA 23)

Afferents to Area 23 (HRP Injection in Area 23)

Afferents to area 23 have been determined by an HRP injection in this part of the cortex in Monkey 3. Since the injections have been made by tangential subpial penetration, the tracks were strictly localized in the grey matter. No lesion of the underlying white fibres could be observed. Diffusion of HRP was found to extend throughout the major part of area 23 except for its most rostral part, but did not involve other adjacent cortical areas.

Cortical labelling. Marked neurons were found in the contralateral area 23, and in some ipsilateral cortical areas shown in fig. 1. Most of them were of the pyramidal type; they were found mainly in superficial cortical layers (III) (fig. 2) but some were in layer V.

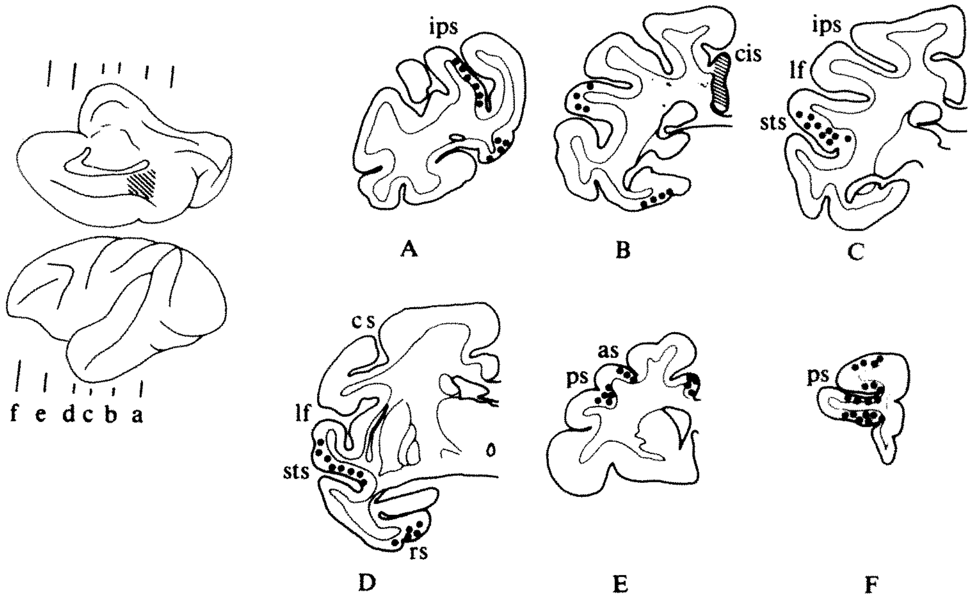

FIG. 1. Distribution of retrogradely HRP-labelled neurons (black spots) indicated at different levels of the cortex following HRP injection in the posterior cingulate area 23 (hatching). (*See overleaf for abbreviations.*)

List of Abbreviations in Text and Figs.

AM = anteromedial nucleus
Am (bl) = basolateral nucleus of the amygdala
as = arcuate sulcus
AV = anteroventral nucleus
C = nucleus centralis
CdN = caudate nucleus
cig = cingulate gyrus
cis = cingulate sulcus
CL = central lateral nucleus
Cla = claustrum
CM = nucleus centrum medianum
cs = central sulcus
CSL = nucleus centralis superior lateralis
GL = lateral geniculate nucleus
GM = medial geniculate nucleus
ips = intraparietal sulcus
LD = laterodorsal nucleus
lf = lateral fissure
LI = nucleus limitans
MD = mediodorsal nucleus
Nas = nucleus accumbens septi
NP = pontine nuclei
PCN = paracentral nucleus
pg = parahippocampal gyrus
PI = inferior pulvinar
PM = medial pulvinar
PO = oral pulvinar
ps = principal sulcus
Put = putamen
rs = rhinal sulcus
SG = suprageniculate nucleus
sts = superior temporal sulcus
VA = ventral anterior nucleus
VL = ventral lateral nucleus
VLps = ventral lateral nucleus (pars postrema)
VPL = ventro-postero-lateral nucleus

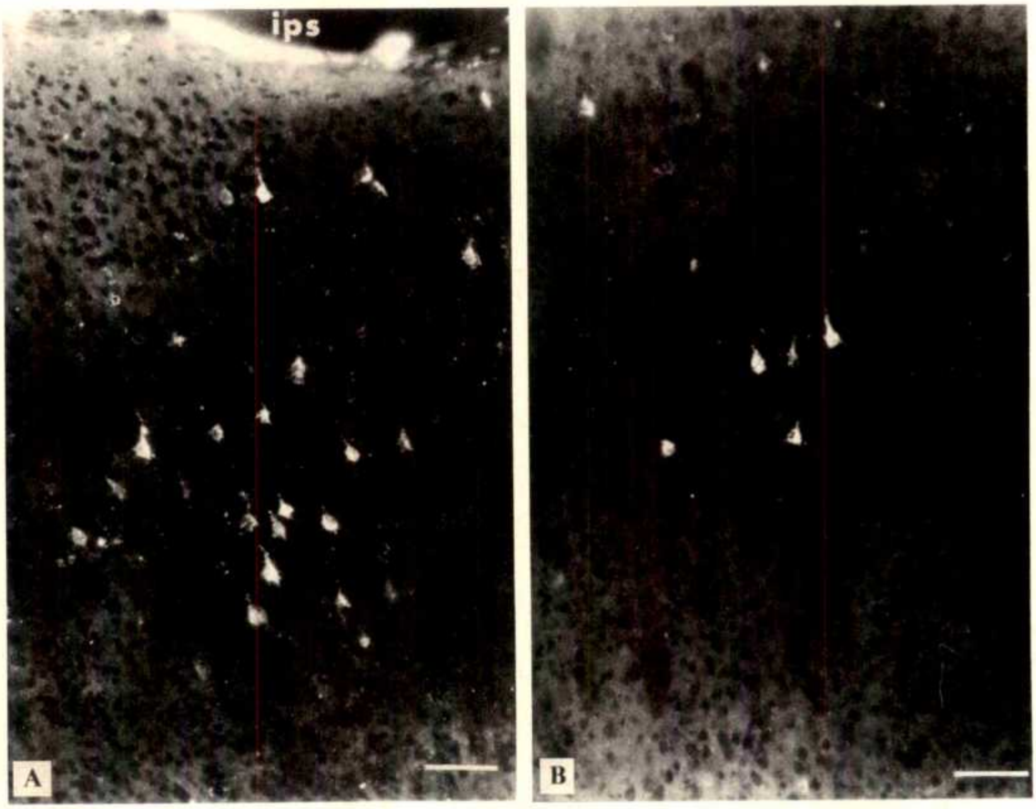

FIG. 2. Examples of HRP-positive cortical neurons in dark field illumination. Bar = 0.2 mm. A, marked pyramidal neurons in the depth of the intraparietal sulcus and B, in the parahippocampal gyrus.

There were numerous HRP positive cells in the caudal part of the intraparietal sulcus (fig. 2A). They were localized in the depth of the posterior bank of the sulcus, which is part of parietal area 7.

Marked cells were seen on the convexity of the superior temporal gyrus which, according to Brodmann's map corresponds to area 22. More rostrally, this labelling invaded the upper bank of the superior temporal sulcus.

The ventromedial temporal cortex was heavily labelled. Caudally, marked cells were found in the cortical area medial to the occipitotemporal sulcus (areas TF and TH of von Bonin). More rostrally labelling was observed in the parahippocampal gyrus (fig. 2B); most of the HRP positive neurons were seen in the cortex medial to the rhinal sulcus, that is, in the entorhinal cortex (area 28) but some of them were found in the perirhinal cortex, lateral to the rhinal sulcus (area 35).

In the frontal lobe, marked cells were observed in the rostral part of the cingulate gyrus (area 24); the fundus and the two banks of the sulcus principalis (area 46) were heavily labelled; the upper aspect of the frontal lobe (area 9) and the orbital frontal cortex (areas 10, 11) also contained HRP-positive cells, as well as the inferior edge of the dorsal arcuate sulcus (area 8).

Thalamic labelling. Thalamic labelling was strictly ipsilateral, as shown in fig. 3, and was mainly concentrated in two thalamic nuclear groups. Numerous positive

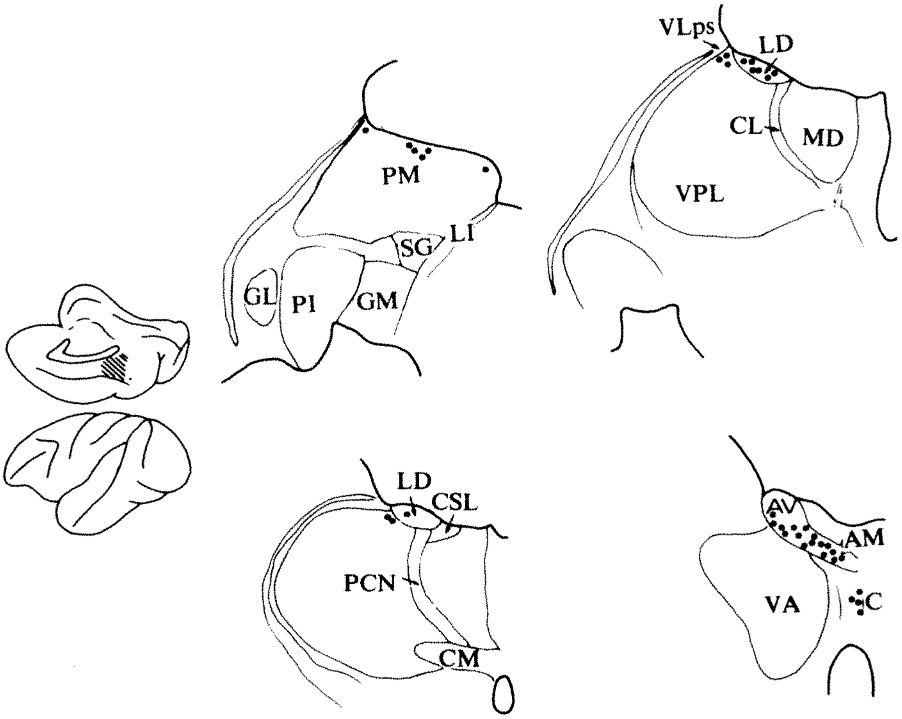

FIG. 3. Distribution of retrogradely HRP-labelled neurons (black spots) at different levels of the thalamus following injection of HRP into the posterior cingulate area 23.

cells were observed in the laterodorsal nucleus, all along its full extent. More rostrally in the anterior thalamus, the anteroventral as well as the anteromedial nucleus contained many marked neurons. The medial pulvinar (caudal part), and, among the midline nuclei, the nucleus centralis exhibited some labelled cells, as did the small pars postrema of the ventral lateral nucleus.

Efferent Projections from Area 23

Projections from area 23 have been determined by an injection of radioactive amino acids in the caudal cingulate gyrus of a cynomolgus macaque (Monkey 1). Some of the cortical projections were confirmed by retrograde transport of HRP (Monkeys 6 to 13).

1. *Autoradiographic Technique*

In the autoradiographic experiment (Monkey 1), two small injections of amino acids were performed; they were found to be close to each other and localized in the grey matter. Labelled neuronal somata, which are known to determine the extent of the spread of injected amino acids, invaded the cingulate gyrus over an extent of 2 mm just above the splenium of the corpus callosum; they were never found in the cingulate sulcus. Thus although area 23 was not totally injected, the injection field was strictly limited to this area.

Three main fasciculi of labelled fibres, represented by linear grain arrangement, could be seen arising from the injection field, one going through the corpus callosum, one directed ventrally to the corona radiata, and a third one directed dorsally to the cortex of the medial aspect of the hemisphere above the cingulate sulcus. Moreover, the cingulum bundle was found to be labelled on its whole course through the cingulate gyrus.

Cortical projections. Intense labelling was observed in the symmetrically-placed contralateral cingulate cortex, where terminals appeared to be distributed in the upper and deeper laminæ of the cortex. This was the only contralateral cortical labelling observed in this animal.

Labelling was found in the cingulate gyrus, extending to the anterior cingulate area 24 and decreasing progressively from the injection site to the rostral end of the gyrus (fig. 4).

Above the cingulate sulcus, the cortex of the medial aspect of the hemisphere had a heavy concentration of grains, distributed in the more superficial and in the deeper layers of the cortex. This labelling was found to involve the medial aspect of the posterior parietal areas and the paracentral lobule, and to extend well forward from the level of the injection site into the inner aspect of area 6 known as the supplementary motor area.

In the temporal lobe, patches of grains were observed in the dorsal bank of the superior temporal sulcus (fig. 4) extending rostrally up to the level of the uncus. The labelled terminals were distributed in a columnar arrangement, forming vertical stripes in the cortex (fig. 5B).

Marker was found in the parahippocampal gyrus (fig. 4, fig. 5C) occupying fibres of the white matter predominantly in the caudal part and invading the grey matter in the more rostral part. Patches of grains were observed close to the hippocampal fissure in the presubiculum and subiculum and more ventrally in the entorhinal cortex (areas 49 and 35).

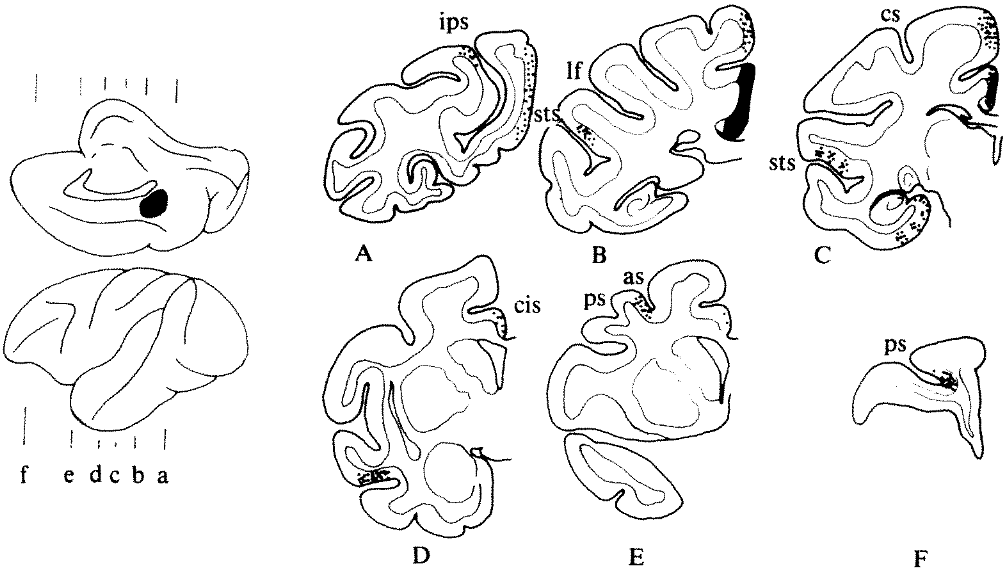

FIG. 4. Distribution of labelled terminals (black dots) at different levels of the cortex following radioactive amino acid injection (in black) in the posterior cingulate area 23.

In the frontal lobe (fig. 4) patches of grains were found in the ventral bank of the arcuate sulcus. More rostrally another accumulation of grains was seen in the depth of the sulcus principalis (fig. 5A) close to the fundus (area 46).

Thalamic projections. The thalamus was labelled only on the ipsilateral side (fig. 6). The medial pulvinar (PM) exhibited dense patches of grains in its caudal and dorsal part (fig. 5D). There seemed to be a sizeable projection from area 23 to the laterodorsal nucleus (LD). Almost the total area of this nucleus was occupied with silver grains. Moreover the fibres of the capsule of LD were clearly labelled. In the anterior thalamus grains were observed mainly in the anteroventral nucleus (AV) (fig. 5E), some of them invading the anteromedial nucleus (AM).

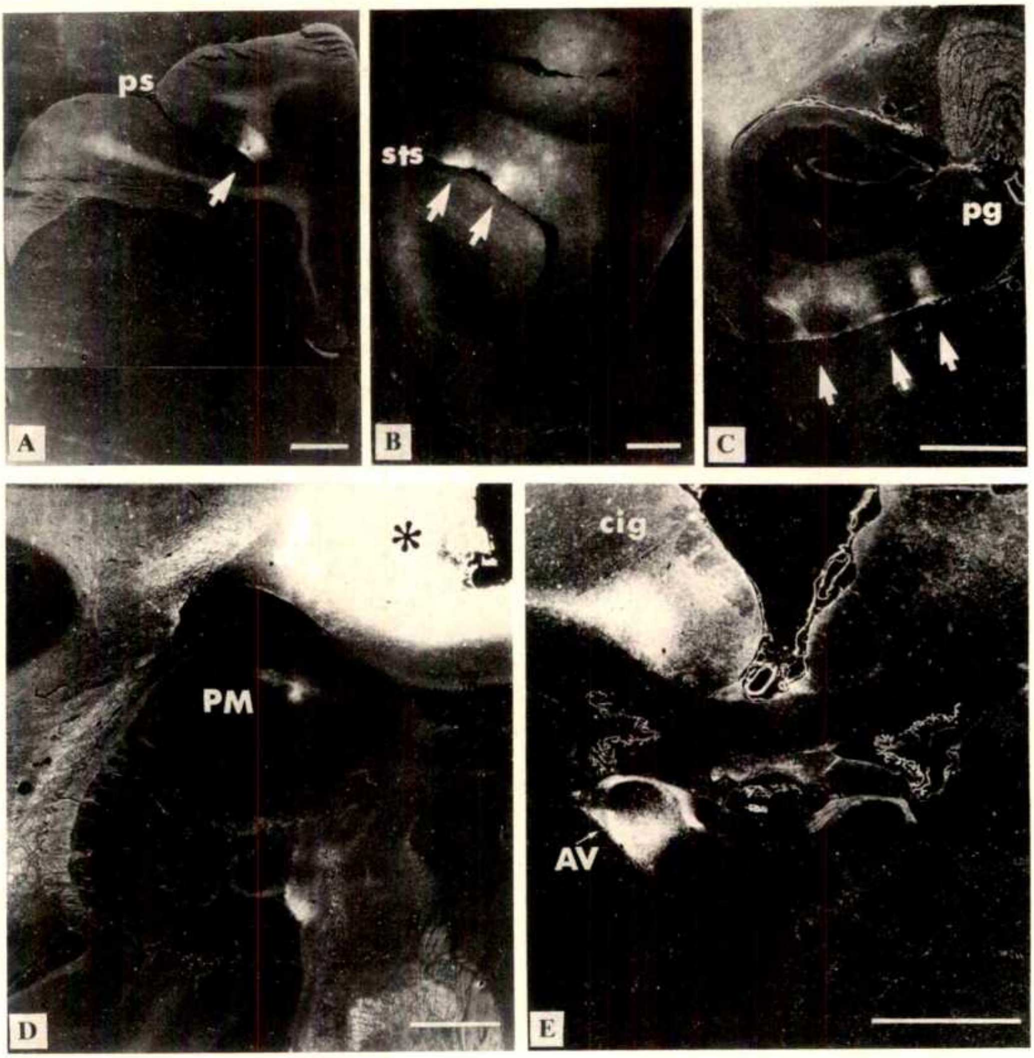

FIG. 5. Different sites of labelled terminals observed after radioactive amino acid injection in the posterior cingulate area 23. Dark field illumination photomicrographes. Bar = 2 mm. Frontal sections, A, of the frontal pole with grains in the depth of the sulcus principalis (ps); B, through the superior temporal sulcus (sts); C, through the parahippocampal gyrus (pg) exhibiting a columnar arrangement of the grains (arrows); D, at the level of the site of injection (asterisk), showing a focus of grains in the medial pulvinar (PM); E, through the anterior thalamus where the ipsilateral anteroventral nucleus (AV) is labelled.

Pontine projections. The projections of area 23 to the ipsilateral griseum pontis formed multiple small and sharply defined foci. These very dense patches were mainly distributed in the lateral part of the pons (fig. 6).

Basal ganglia projections. The caudate nucleus (CdN) was observed to contain marker (fig. 7). Rostrally, in the ipsilateral head of the CdN a heavy concentration of

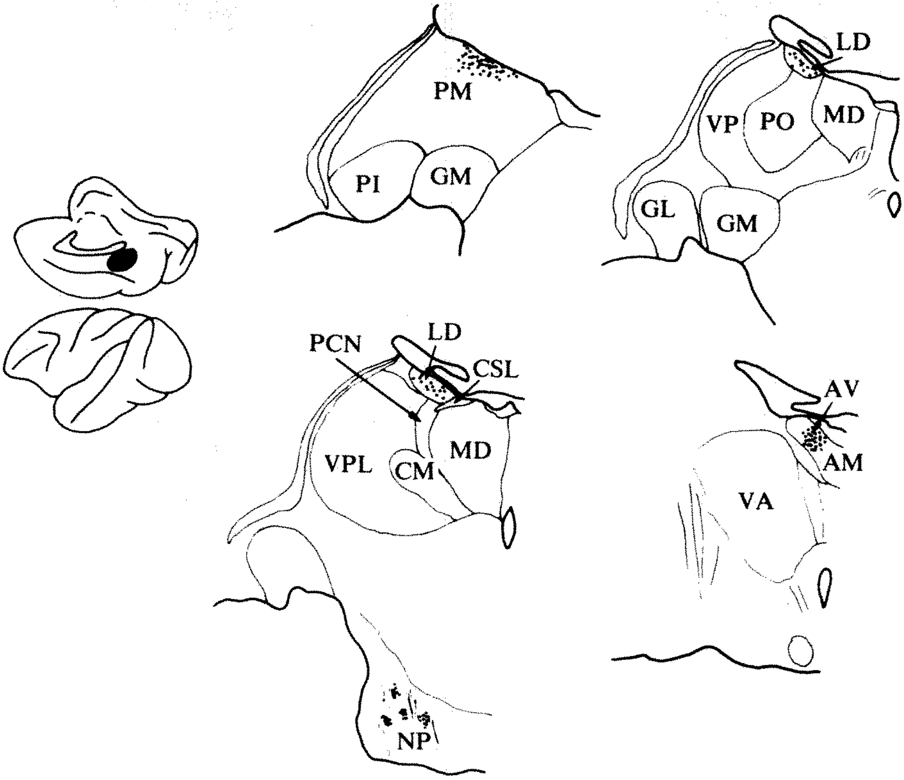

FIG. 6. Distribution of labelled terminals (black dots) at different levels of the thalamus after radioactive amino acid injection (in black) of area 23.

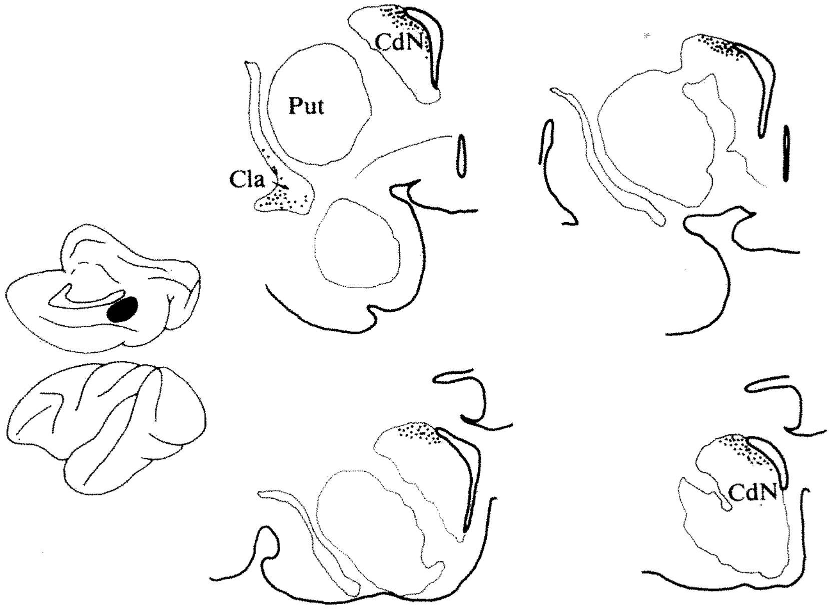

FIG. 7. Distribution of labelled terminals (black dots) at different levels of the basal ganglia after radioactive amino acid injection (in black) of area 23.

grains was localized in the border of the nucleus with the lateral ventricle. Labelled terminals invaded the body of the nucleus and vanished progressively caudalward. Very sparse labelling occurred in the contralateral head and body of the CdN mainly localized close to the border of the lateral ventricle. The ventral part of the claustrum was also found to be labelled but not the pallidum or the putamen.

2. *HRP Technique*

Some of the cortical projections from area 23 described above were also demonstrated by the HRP technique (fig. 8). Three HRP experiments involving injections in area 7 (Monkeys 6, 7 and 8) resulted in an abundant labelling of the ipsilateral posterior cingulate cortex, where HRP-positive pyramidal neurons could be observed. Labelling also occurred, although more discretely, in the contralateral area 23. Few marked cells were found in ipsilateral area 23 following an HRP injection in the superior temporal gyrus, i.e. area 22 (Monkey 9). In contrast, no labelling of the cingulate gyrus was seen after injection in the inferior temporal gyrus, i.e. area 21 (Monkey 10). Three HRP experiments were performed in the superior temporal sulcus, one in the posterior ventral bank (Monkey 11), one in the posterior dorsal bank (Monkey 12) and one in the anterior dorsal bank (Monkey 13). This latter injection was the only one to result in labelling of the ipsilateral posterior cingulate gyrus. It is noteworthy that the injected area in this case overlapped the radioactively-labelled zone of the superior temporal sulcus in the monkey which received tritiated amino acids in area 23 (Monkey 1).

II. ANTERIOR CINGULATE CORTEX (AREA 24)

Afferents to Area 24 (HRP Injection in Area 24)

The projections to area 24 were determined by HRP injections in the rostral cingulate gyrus, performed in two animals (Monkeys 4 and 5). In both cases, the needle track was confined to the grey matter, not injuring the underlying white fibres.

Cortical labelling. Except for the presence of a very small number of marked neurons in the contralateral area 24, labelling of the cortex was strictly ipsilateral to the injection side (fig. 9).

A few HRP-positive neurons were observed in the most dorsal part of the superior temporal sulcus, in its anterior bank, which belongs to the border of area 7, according to Brodmann's map.

Marked cells were distributed in the gyrus and in the cingulate sulcus of the granular posterior cingulate cortex (area 23).

In the frontal lobe, marked cells were found in the depth of the arcuate sulcus, along its whole length, as well as in the fundus of the sulcus principalis.

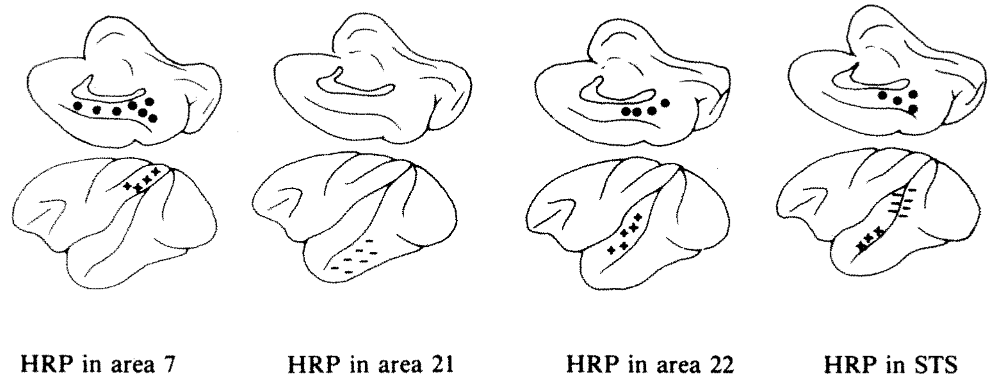

FIG. 8. Labelling of the cingulate gyrus following injection of HRP into the associative sensory areas 7, 21, 22 and into the superior temporal sulcus. HRP injection resulting in positive labelling of the cingulate cortex (+); HRP injection resulting in negative labelling of the cingulate cortex (−); HRP-positive cell (●).

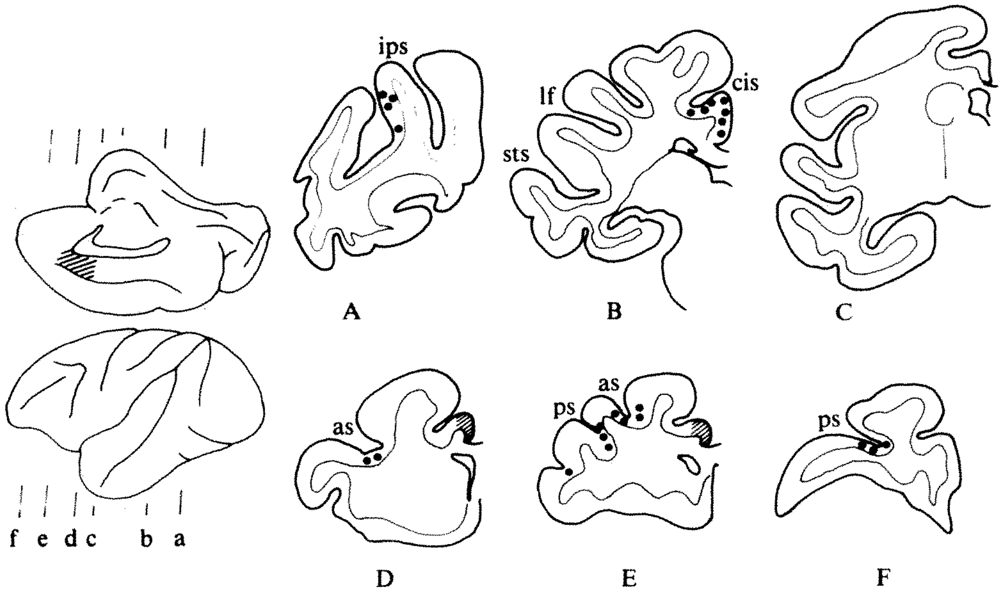

FIG. 9. Distribution of retrogradely HRP-labelled neurons (black dots) at different levels of the cortex after injection of HRP into the anterior cingulate area 24 (hatching).

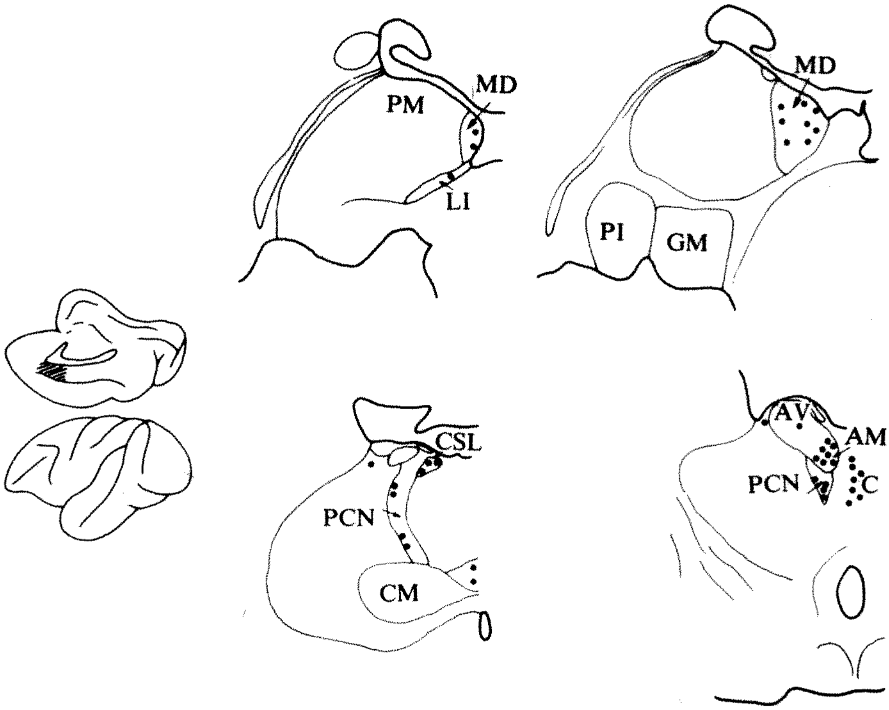

FIG. 10. Distribution of retrogradely HRP-labelled neurons (black spots) at different levels of the ipsilateral thalamus after injection of HRP into the anterior cingulate area 24 (hatching).

Thalamic labelling. Only ipsilateral thalamic nuclei contained labelled neurons (fig. 10). In the mediodorsal nucleus (MD) a sizeable number of HRP-positive cells was found, mainly in the caudal half. According to Olzewski's atlas, these marked neurons would belong to the parvocellular, magnocellular and densocellular parts of the MD. Among the intralaminar nuclei, the nucleus limitans, the central lateral (CL) and the paracentral nucleus (PCN) as well as the nucleus centralis superior lateralis (CSL) exhibited many labelled neurons. The nucleus centralis (C) of the midline group of nuclei was found to contain marker. In the anterior thalamus, HRP-positive cells were seen in the anteromedial nucleus (AM). A group of densely packed labelled neurons were seen in the extreme dorsolateral part of the ventral anterior nucleus (VA).

Efferent Projection from Area 24

1. *Autoradiographic Experiment*

The injection of tritiated amino acids in the rostral cingulate cortex of a Macaca mulatta (Monkey 2) was found to be localized in the agranular cortex; labelled somata extended over a few millimetres in the cortex overlying the genu of the corpus callosum. From the injection field, three main groups of labelled fibres could be seen streaming away, one to the corpus callosum, one to the cortex of the medial aspect of the hemisphere above the cingulate sulcus, one to the external capsule, giving off a contingent of fibres into the internal capsule and the cingulum bundle.

Cortical labelling. In this experiment, the only contralateral labelling was in the cingulate gyrus symmetrical to the injected region.

In the ipsilateral hemisphere, patches of grains were found in the anterior cingulate gyrus with a concentration decreasing forward and backward from the injection site; caudally the grains invaded area 23. A great number of labelled terminals was observed in the cortex of the medial aspect of the hemisphere above the cingulate sulcus, this labelling involving the medial aspects of areas 9, 6 and 4.

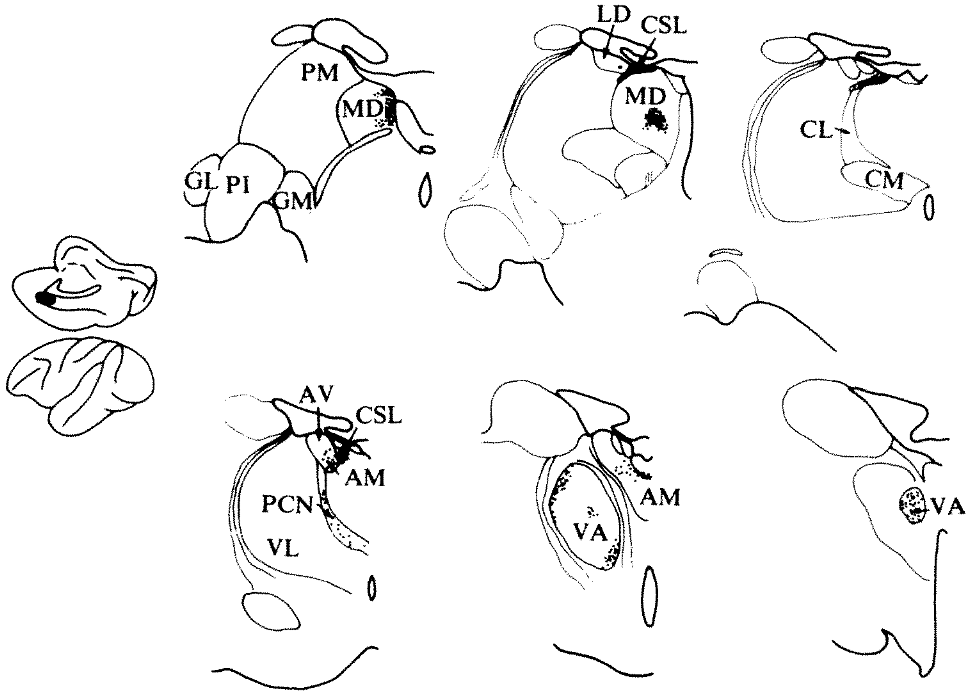

FIG. 11. Distribution of labelled terminals (black dots) at different levels of the thalamus after radioactive amino acid injection (in black) in the anterior cingulate area 24.

Thalamic labelling. Only the ipsilateral thalamus was labelled (fig. 11). In the extreme caudal part of the mediodorsal nucleus, the labelling was medial and occupied the major part of the nucleus. More rostrally, it shifted to a more central position. Then, the rostral third of the MD was free of labelled terminals (fig. 12A–D).

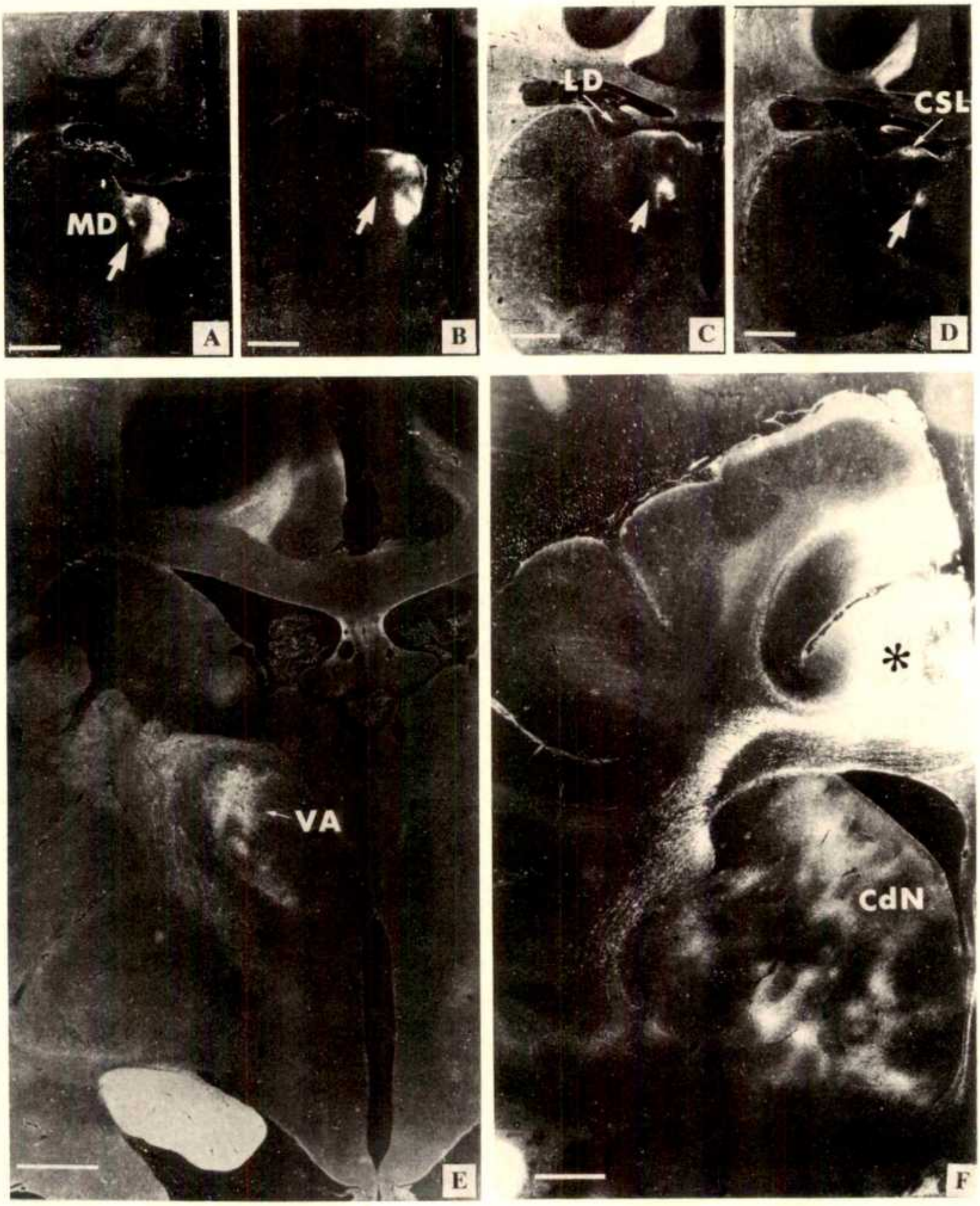

FIG. 12. Different sites of labelled terminals observed after radioactive amino acid injection in the anterior cingulate area 24. Dark field illumination photomicrographes of frontal sections. Bar = 2 mm. A–D, evolution of the labelling of the mediodorsal nucleus (MD) from A, a caudal to D, a more rostral level. Note the presence of grains in the nucleus centralis superior lateralis (CSL) in D. E, rostral end of the ventral anterior nucleus (VA); F, high density of grains, encountered in the caudate nucleus.

According to Olzewski's atlas, it would seem that the densocellular and parvocellular divisions and a portion of the magnocellular division of the MD was involved in the labelling.

In the intralaminar group, the nucleus centralis superior lateralis (CSL) was clearly filled with labelled terminals (fig. 12D) over its whole sagittal extent. Grains occupied a great part of the thin curved figure of the central lateral (CL) and the paracentral (PCN) nucleus. Of the midline nuclei, the nucleus centralis contained some labelled terminals.

Silver grains in the anterior group of nuclei were predominantly localized in the anteromedial nucleus (AM).

Patches of labelled terminals were observed in the ventral anterior nucleus (VA) distributed unevenly and present also in the rostral end of the nucleus (fig. 12E).

No labelled terminals were seen in the pons.

Projections to the basal ganglia. The striatum can be considered as a main projection zone of the anterior cingulate gyrus (fig. 13). Fibres of the external and the internal capsules were clearly delineated by the marker. Rostrally, the head of the ipsilateral caudate nucleus (CdN), and the ipsilateral putamen (Put) had a great quantity of silver grains, distributed all over these nuclei and sometimes packed into patches of more intense concentration (fig. 12F). Labelled fibres were found running through these nuclei. The head of the contralateral CdN and the contralateral Put

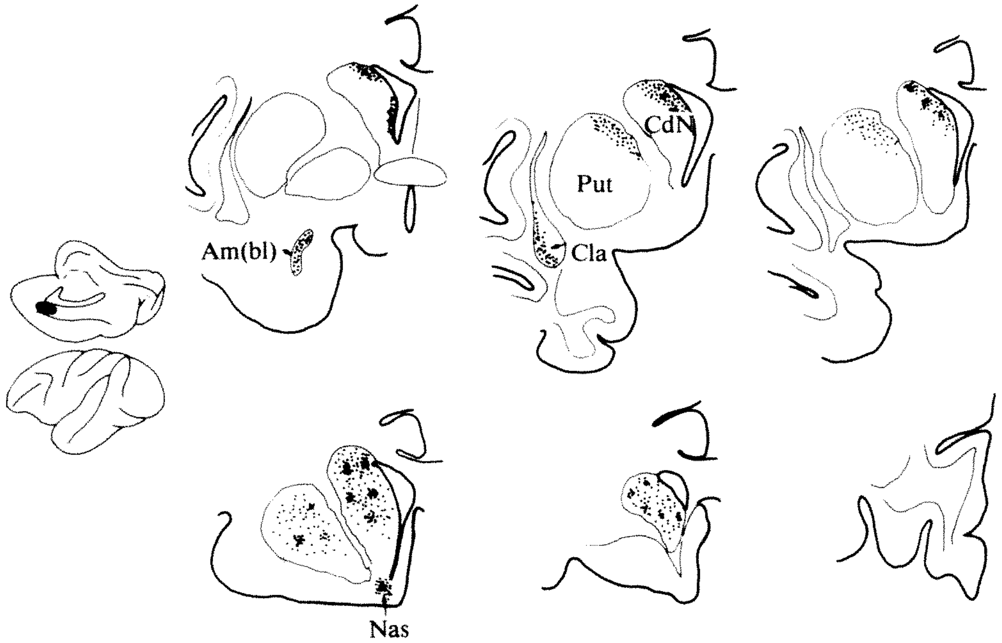

FIG. 13. Distribution of labelled terminals (black dots) at different levels of the basal ganglia after radioactive amino acid injection (in black) in the anterior cingulate area 24.

were also labelled, although less heavily, with the same general pattern as in the ipsilateral basal ganglia (i.e., patches and labelled fibres). The concentration of grains in the CdN was found to decrease caudalward and to vanish completely in the body of the nucleus. The labelling of the putamen dropped caudally at the coronal plane of the pallidum which was itself always free of grains.

Terminal labelling was also present in the ventral part of the claustrum.

Projections to the nucleus accumbens septi and the amygdala. The nucleus accumbens septi, which is medial and ventral to the head of the caudate nucleus, contained a great number of labelled terminals.

In the amygdaloid complex, the oblong shape of the basolateral nucleus appeared to be entirely filled with marked terminals.

2. *HRP Technique*

Efferent cortical projections from area 24 have also been demonstrated by HRP injections in the cortex (fig. 8). Following HRP injection in the dorsal part of the inferior parietal lobule (area 7) (Monkeys 6, 7 and 8) labelled neurons were seen in the anterior cingulate as well as in the posterior cingulate areas (*see above*). In contrast, HRP injections in the cortex of the superior (Monkey 9) and inferior temporal gyrus (Monkey 10), as well as in the superior temporal sulcus (Monkeys 11, 12, 13) never resulted in labelling of the anterior cingulate cortex.

DISCUSSION

Anatomical Comments

In most previous studies, the cortical connections of the cingulate gyrus have been described without any reference to the heterogeneity of this area; by contrast, differentiation between areas 23 and 24 is always taken into account when the thalamic or subcortical connections are considered.

Cortico-cortical connections. We have confirmed Vogt, Rosene and Pandya's (1979) recent finding that areas 23 and 24 are interconnected with each other. Besides this tight anatomical coupling, both areas 23 and 24 are connected with the frontal lobe. The medial aspect of the precentral areas 6 and 4 and the cortex of the arcuate sulcus and of the sulcus principalis are interconnected with both cingulate areas, as previously described (Pandya and Kuypers, 1969; Goldman and Nauta, 1977; Künzle, 1978) when area 23 alone is related to the dorsal (area 9) and orbital (area 11) parts of the frontal pole. Concerning this last point, discrepancies already exist in the literature since the orbitofrontal cortex was found to project either to the anterior cingulate gyrus alone (Van Hoesen, Pandya and Butters, 1975) or to both areas 23 and 24 (Pandya and Kuypers, 1969).

Like the frontal lobe, the inferior parietal lobe is connected with both areas 23 and 24. The inferior parietal lobule (area 7) is already known to send projection fibres to the whole cingulate gyrus (Jones and Powell, 1970; Pandya and Kuypers, 1969) and to receive afferents from the whole cingulate cortex (Pandya, Deepak, Domesick, Van Hoesen and Mesulam, 1972; Stanton, Cruce, Goldberg and Robinson, 1977; Mesulam, Van Hoesen, Pandya and Geschwind, 1977). Nevertheless, in our experiments, the connections of area 7 seem to be richer with area 23 than with area 24; this observation is in fact also evident in the illustration of Pandya and Kuypers (1969).

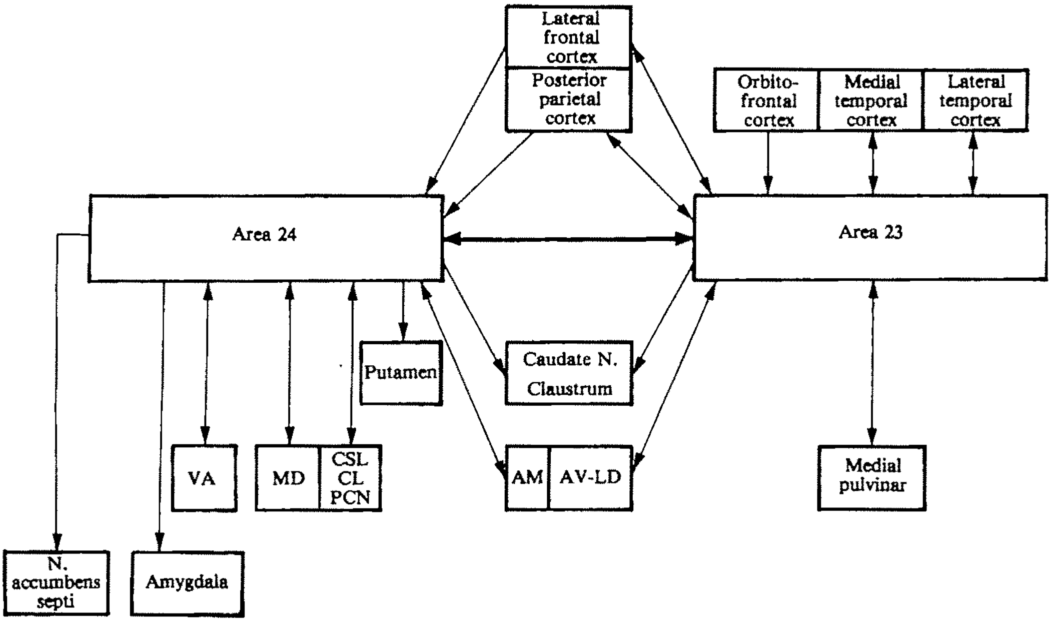

FIG. 14. Schematic representation of the respective connections of areas 23 and 24.

Whereas the frontal and inferior parietal lobes are connected with both the anterior and posterior cingulate cortex, our results demonstrate that area 23 only is connected with the temporal lobe, altogether with its lateral surface, that is, the cortex of the superior temporal gyrus and of the superior temporal sulcus, and with its ventromedial aspect (parahippocampal gyrus). We know of no previous description of connections between the superior temporal sulcus and the cingulate gyrus, although, according to our results, this relationship appears to be quantitatively important. The vertical 'columnar' arrangement of radioactive terminals observed in the superior temporal sulcus, and also in the parahippocampal gyrus, has already been described for cortico-cortical projections as well as for thalamo-cortical ones (Goldman and Nauta, 1977). It is noteworthy that the upper bank of the superior temporal sulcus, which is reciprocally connected with area 23, is the part of this sulcus which, according to Seltzer and Pandya (1978) is a 'zone of converging pathways'. This particular zone is considered as a site of polysensory convergence since it receives projection fibres from the three sensory association cortices (visuosomæsthetic area 7, auditory area 22 and visual associative area 21) (Selzer and Pandya, 1978; F. Mauguière and C. Baleydier, unpublished data).

Area 23 is reciprocally connected with the pre- and parasubiculum and with the entorhinal cortex. The degeneration studies in monkey (Adey and Meyer, 1952; Gardner and Fox, 1948; Pandya *et al.*, 1972) as well as in rat (Raisman, Cowan and Powell, 1965) have already indicated the presence of projection fibres from the cingulate gyrus and from the cingulum to the parahippocampal gyrus. Nevertheless, the use of HRP and of autoradiographic techniques allowed us to demonstrate that this connection concerns specifically area 23.

Subcortical connections. The cingulate gyrus, as a whole, was observed to be related with the so-called limbic nuclei of the thalamus as previously described by Pribram and Fulton (1954), Locke, Angevine and Yakovlev (1961) in man and (1964) in monkey, Siegel, Troiano and Royce (1973) and Niimi (1978) in cat and Domesick (1969) in rat. Area 24 was found to be specifically interconnected with AM and area 23 with AV and LD, and to a lesser extent with AM too. Thus, if one accepts considering LD, because of its afferents from the fornix, as 'the caudal member of the limbic group of thalamic nuclei' (Locke *et al.*, 1964), one may conclude that the limbic thalamic connections of the cingulate gyrus are topologically organized.

Area 24 only sends projection fibres to the basolateral nucleus of the amygdala. Besides this classical anatomical result (Powell, 1978; Pandya, Van Hoesen and Domesick, 1973; Müller-Preuss and Jürgens, 1976; Vogt *et al.*, 1979), we found area 24 to project to the nucleus accumbens septi when area 23 does not.

The intralaminar nuclei and the mediodorsal nucleus are exclusively connected with area 24; no connections of these nuclei with area 23 have been demonstrated in our study. Besides the paracentral and the central lateral nucleus which were already described to be connected with area 24 (Jones and Leavitt, 1974, in rat; Murray, 1966, in cat; Vogt *et al.*, 1979, in monkey), the central superior lateral nucleus deserves a special mention since it was found to be intensely labelled either with HRP or with radioactive material after injection of area 24. The relationship between the MD and the anterior cingulate area is classically admitted (Powell, 1978, in monkey; Siegel *et al.*, 1973, in cat; Domesick, 1969, in rat) although Vogt *et al.* (1979) did observe connections between the MD and both areas 23 and 24.

Area 23 is the only cingulate area to be reciprocally connected with the medial pulvinar. In this context it is interesting to note that there are direct connections between the PM and postcentral sensory association areas (Baleydier and Mauguière, 1977; Mauguière and Baleydier, 1978), and not with any other areas of precentral agranular cortex (Trojanowski and Jacobson, 1974).

The projections of the cingulate gyrus to the basal ganglia have been studied in different species (Showers, 1959; Müller-Preuss and Jürgens, 1976; Powell, 1978; Siegel *et al.*, 1973; Domesick, 1969). However, authors do not come to an agreement concerning the distribution of these projections. In our study, we found them to be particularly dense from area 24 to the caudate nucleus. This prevalence of the connections between area 24 and the structures belonging to the extrapyramidal pathways is coherent with the observation that area 24 was found to be specifically connected with the ventral anterior nucleus of the thalamus.

GENERAL DISCUSSION

Our results lend support to the hypothesis of a functional coupling of areas 24 and 23. Both areas are connected with the limbic thalamic nuclear group and thus fully belong to the system which, in Papez's theory (1937), is supposed to subserve emotional behaviour. In this system area 23 can be regarded as an associative area which receives afferents from and send fibres to other cortical areas known to be sites of polysensory convergence. These areas for which multisensory converging afferents have been anatomically demonstrated are the upper bank of the superior temporal sulcus (Seltzer and Pandya, 1978) and areas 28 and 35 belonging to the perirhinal cortex (Jones and Powell, 1970). Moreover area 23 is reciprocally connected with the medial pulvinar; this thalamic nucleus receives polysensory inputs (Mathers and Rapisardi, 1973) and send afferents to other postcentral areas involved in the integration of sensory processing, that is, Brodmann's areas 7, 21 and 22 (Baleydier and Mauguière, 1977; Mauguière and Baleydier, 1978). Area 24 is devoid of such thalamic and cortical sensory afferents except those from area 7 (*vide infra*); in consequence area 24 might receive through its connections with area 23 the integrated sensory inputs necessary for the control of emotional behaviour.

According to the view of Vogt *et al.* (1979) one may assume that nociceptive inputs probably reach area 24 without previous synaptic relay in the posterior cingulate cortex since the densocellular part of the mediodorsal nucleus and the centralis lateralis nucleus, which are known to receive fibres from the spinothalamic tract in monkeys (Mehler, Feferman and Nauta, 1960), have been found to be reciprocally connected with area 24 and not with area 23 in our study.

In the same way that most non-painful sensory inputs may enter the cingulate gyrus through area 23, most of the behavioural and autonomic reactions, which form the emotional output of the cingulate gyrus, may arise from area 24 and reach the amygdala, the nucleus accumbens septi and the mediodorsal nucleus of the thalamus. The basolateral nucleus of the amygdala and the mediodorsal nucleus are known to be relays towards the hypothalamus and, according to Mesulam and Geschwind (1978), the nucleus accumbens septi is connected with the substantia innominata of the hypothalamus. In our study these three nuclei have been found connected with area 24 but not with area 23.

For memory processes, a similar kind of functional coupling between areas 24 and 23 could be envisaged, providing that one accepts the hippocampal memory hypothesis, since both areas receive hippocampal input *via* the fornix. However, some experimental results in the monkey (Schulman, 1964) and clinical data in man, recently reviewed by Horel (1978), tend to demonstrate that a bilateral and complete destruction of the mediodorsal nuclei can produce deficits in learning and memory. According to Horel (1978) the magnocellular part of the mediodorsal nucleus of the thalamus receives fibres from the lateral temporal neocortex through the temporal stem, and is connected with the orbital and medial frontal cortex. Bilateral lesions of the temporal neocortex (Horel and Misantone, 1975) and bilateral section of the temporal stem (Horel and Keating, 1969; Horel and Misantone, 1974) may impair memory processes in monkeys. Although the mnemonic role of the lateral temporal neocortex in monkeys has been discussed mainly on the basis of degraded performance in visual discrimination tasks after lesions of the inferotemporal cortex (Mishkin and Pribram, 1954; Mishkin and Oubre, 1976; Mishkin, 1972; Dean, 1974; Dean and Weiskrantz, 1974; Delacour, 1977), one may suggest that the cause of these troubles could be an interruption of the connections between the lateral temporal cortex and the frontal lobe, the anterior cingulate gyrus being included in the latter. The mediodorsal nucleus of the thalamus is, among others, a possible site for this disconnection. Should this hypothesis be verified, a preferential role in memory processes would be assigned to the anterior part of the cingulate gyrus, since we have shown that area 24 is reciprocally connected with the mediodorsal nucleus whereas area 23 is not. Nevertheless, input from the lateral temporal cortex may also reach the anterior cingulate gyrus by way of the connections we have demonstrated between the superior temporal gyrus and area 23. Then, if the lateral temporal cortex is more essential for memory processing than the hippocampus, as proposed by Horel (1978), both cingulate areas may have complementary functions in memory.

The concept of a functional coupling between areas 24 and 23 in the control of mechanisms underlying exploratory behaviour and attention towards sensory stimuli is also supported by our anatomical data. Both areas are connected with the part of the lateral frontal pre-motor cortex known as the 'frontal eye field', and with the part of the posterior parietal area 7 which, on the basis of microelectrode electrophysiological studies in monkeys, is known to be involved in the control of eye and hand movements towards significant visual stimuli (Hyvärinen and Poranen, 1974; Mountcastle, Lynch, Georgopoulos, Sakaya and Acuna, 1975; Lynch, Mountcastle, Talbot and Yin, 1977; Robinson, Goldberg and Stanton, 1978). We found the reciprocal connections of area 7 with the cingulate gyrus to be more numerous for area 23 than for area 24. This result supports the hypothesis that area 23 is the sensory 'associative' area of the cingulate gyrus and, as such, may play a role in the cognitive processes of sensory attention. We found that area 24 is connected with thalamic intralaminar nuclei (CL, CSL), the destruction of which may lead to a lateralized neglect phenomenon in cat (Orem, Schlag-Rey and Schlag, 1973) in monkey (Watson, Miller and Heilman, 1978) and probably in man too (Watson and Heilman, 1979). This experimental neglect phenomenon is very close to that observed after unilateral ablation of the anterior cingulate gyrus (Watson *et* *al.*, 1973) and may be interpreted as an hemispatial hypokinesia, since Watson *et al.* (1973, 1978) have demonstrated that it is the response towards the neglected field which is disrupted, and not the appreciation of the stimulus. It may be suggested that the control of the arousal reaction and the programming of kinetic responses to sensory stimulation could be specific functions of the anterior cingulate area 24. Two of our anatomical results lend substance to this idea. First, area 23 has not been found to be connected with the intralaminar nuclei of the thalamus, and secondly, area 24 sends dense projections to the basal ganglia (caudate nucleus, claustrum and the putamen) and to the ventral anterior nucleus of the thalamus, whereas the projections of area 23 to the 'extrapyramidal' pathways are restricted to the head of the caudate nucleus and the claustrum.

We may conclude that the organization of the anatomical connections of the cingulate gyrus is concordant with the general scheme proposed by Jones and Powell (1970) of an hierarchical arrangement of coupled pre- and postcentral areas within the cerebral cortex. According to this concept area 23 could be considered as the site of a multimodal sensory convergence and area 24 as a highly specialized motor area. This extrapolation would be misleading if we fail to take into account the fact that the cingulate gyrus is not only involved in sensory integration and motor programming, like the other pre- and postcentral coupled areas described by Jones and Powell (1970). We hope to have demonstrated, on an anatomical basis, that the functional coupling of areas 24 and 23 remains a valuable hypothesis when one considers the probable peculiar function of the cingulate gyrus as an interface between emotion and intelligence.

SUMMARY

According to most behavioural, electrophysiological, and clinical studies, the cingulate gyrus is widely thought to be involved in regulation of emotional life, reactivity to painful stimuli, memory processing, and attention to sensory stimuli. Anatomically the cingulate cortex is composed of two distinct areas numbered 24 and 23 in Brodmann's classification.

We have investigated the connections of the cingulate gyrus in monkeys, using horseradish peroxydase and radioautographic techniques, in order to verify the hypothesis of an anatomical complementarity of these cytoarchitectonic subdivisions. The posterior cingulate gyrus (area 23) is specifically connected with the associative temporal cortex, the medial temporal and orbitofrontal cortices, and with the medial pulvinar. The anterior cingulate gyrus (area 24) is related to the intralaminar, mediodorsal, and ventral anterior thalamic nuclei, the amygdala, and the nucleus accumbens septi. The two cingulate areas were found to be interconnected and to have, in common, connections with the 'limbic' thalamic nuclei (AM, AV, LD), the caudate nucleus, the claustrum, the lateral frontal and the posterior parietal (area 7) cortices.

It is suggested that the two cingulate areas could be anatomically and functionally coupled in the same way as are the postcentral areas with the precentral motor cortex.

The contribution of these anatomical data to the understanding of the function of the cingulate gyrus is discussed.

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AMMONIA: ASSESSMENT OF ITS ACTION ON POSTSYNAPTIC INHIBITION AS A CAUSE OF CONVULSIONS

by J. F. ILES[1] *and* J. J. B. JACK

(From the University Laboratory of Physiology, Oxford)

INTRODUCTION

ELEVATED cerebral ammonia concentrations are associated with disorders of nervous function. (In this paper we follow the convention that ammonia (Amm.) refers to the sum of ammonium ion (NH_4^+) and ammonia gas (NH_3).) Administration of ammonium salts or endogenous production of ammonia, as the result of a biochemical anomaly, lead to lethargy, convulsions, ataxia, and coma (Colombo, 1971). A role for ammonia in some diseases with these symptoms has therefore been suspected. Furthermore, since convulsive activity itself elevates cerebral ammonia (Richter and Dawson, 1948; Torda, 1953), ammonia could contribute to convulsions of other ætiology. However, ammonia levels have not always correlated well with the severity of nervous symptoms (but *see* Brusilow, Tinker and Batshaw, 1980). Acceptance of a role for ammonia has also been inhibited by the paucity of evidence for specific physiological actions at the concentrations found in disease.

Four main actions of ammonia on the nervous system have been described: changes in intracellular pH (*see* Thomas, 1974; Boron and De Weer, 1976), shifts in electrolytes between intracellular and extracellular compartments (Benjamin, Okamoto and Quastel, 1978), interference with biochemical reactions (Hindfeldt and Siesjo, 1971*b*, Zieve and Nicoloff, 1975; Siesjo, 1978), and depression of hyperpolarizing inhibition in both motoneurons (Lux, Loracher and Neher, 1970; Llinás, Baker and Precht, 1974) and cortical neurons (Raabe and Gumnit, 1975). The consequences of the first three actions are not clear, but it is natural to assume that depression of postsynaptic inhibition is an explanation for the acute convulsant action of ammonia by analogy with the effects of strychnine.

Lux and his colleagues (1970) noted that the action of ammonia on postsynaptic inhibition of spinal motoneurons was not identical to that of strychnine. They observed a progressive decline in the reversal potential for inhibition from the normal value (hyperpolarized with respect to the resting potential) to the resting potential itself, thus removing the hyperpolarizing component of inhibition alone. Nevertheless, loss of this component of inhibition would be expected to reduce the 'effectiveness' of central inhibition (*see* Jack, Noble and Tsien, 1975, pp. 197–213).

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[1] Present address: Department of Zoology, South Parks Road, Oxford OX1 3PS.

None of the studies of the depressant effect on central inhibition monitored ammonia concentrations, so it is not certain that the effective range corresponds to that reached in disease. The present experiments were undertaken to examine the action of known levels of ammonia on postsynaptic inhibition in the central nervous system of the cat.

We have determined the relationship between extracellular (cerebrospinal fluid) ammonia concentration and depression of hyperpolarizing inhibition. In discussing this result we draw attention to uncertainties in the normal distribution and metabolism of ammonia in the brain. We suggest that a clearer understanding of these matters is required in order to assess the role of ammonia in the production of neurological disorders. A brief report of some of the experimental results has been published (Iles and Jack, 1978).

METHODS

The experiments were designed to record inhibitory postsynaptic potentials (ipsps) in cat motoneurons. The transmembrane current required to reverse the ipsp was estimated and used as a measure of the strength of inhibitory hyperpolarization. Following elevation of cerebral ammonia to a new steady value by infusion of ammonium salts, inhibitory hyperpolarization was estimated again. Comparison of the two values defines the response to ammonia.

(1) *Electrophysiological Techniques*

Young adult cats (weight about 2 kg) were anæsthetized with pentobarbitone (Sagatal 40 mg/kg intraperitoneally with supplements intravenously when required). The animals respired spontaneously in most experiments, but if forced ventilation was needed we monitored end-tidal CO_2 (maintained at 3.5 per cent). Body temperature was kept between 35 and 38° C by radiant heat: Dextran was routinely given (10 ml i.p.) with supplements i.v. if the blood pressure fell below 80 mm Hg. The nerves to quadriceps, posterior biceps-semitendinosus, gastrocnemius-soleus and sometimes also the deep peroneal nerve were exposed in the left hind limb, cut peripherally and prepared for stimulation. The spinal cord was exposed by a laminectomy from L3 to L7. Cord and leg dissections were covered in warm liquid paraffin.

Intracellular records were taken from motoneurons in L7 identified by antidromic invasion. All the records analysed were from posterior biceps and semitendinosus motoneurons, but the ability to identify those projecting to the other muscles facilitated location of the motor cell columns.

Microelectrodes were pulled from glass capillaries containing a fibre and then backfilled with 1.5 mol/l potassium citrate solution with the addition of 5 per cent of 1.5 mol/l potassium chloride. This low chloride filling solution was chosen to minimize any effect of chloride leakage from the microelectrode on the intracellular chloride levels and thus on the reversal potential for inhibition, which is chloride sensitive. The electrodes were stored in this solution and then bevelled until the impedance (measured at 70 Hz) fell to 6–7 MΩ. This value was found to be optimal for stable recording and for good current passing characteristics. Just before use the outside of each electrode was rinsed, dried, dipped in 4 per cent 3,3,3-(trifluoropropyl) trimethoxysilane in carbon tetrachloride and allowed to dry again. The silicone treatment was intended to facilitate sealing between the electrode and the motoneuron membrane.

The recording amplifier possessed the facility for passing constant current pulses through the electrode. Pulse duration was 70 ms which is long, relative to the range of motoneuron time constants (*see* Jack, Miller, Porter and Redman, 1971). Inhibitory postsynaptic potentials (ipsp) were produced by stimulating the quadriceps nerve at group I strength. The ipsp was superimposed towards the end of the current pulse. In order to avoid recording the large shifts of potential caused by currents flowing through the microelectrode resistance, a second signal produced by passing the same current through a resistance approximating that of the microelectrode was subtracted. In addition a suppressor unit (Eccles, Eccles and Ito, 1964) reduced amplifier gain until just before the ipsp occurred. The ipsp's recorded at different levels of polarizing current were averaged in a Biomac (Data Laboratories Ltd.). This permitted accurate (better than 5 per cent) measurement of the current just reversing the ipsp. Motoneuron input resistances were estimated by the spike height method (Frank and Fuortes, 1956) using the same current pulses and averaging methods.

In order to pass quite large currents through the microelectrode the recording amplifier (LH0042C, National Semiconductors; modern equivalent LM355N) was not arranged in the usual voltage follower mode. Instead the microelectrode and animal preparation were in the feedback loop, giving a gain of -1. In this mode the input capacity of the amplifier has much less degrading effect on the frequency response of the circuit, and the only factor limiting the current passing capacity of the circuit (and its constancy in the face of changing microelectrode resistance) is when the output voltage of the amplifier reaches the voltage of the amplifier power supply. A disadvantage of this circuit is that the preparation cannot be grounded, but it is held at very low impedance (to ground) and we have had no problems with A.C. pick-up. The circuit was designed and built by Mr W. Laycock of this Laboratory, from whom further details may be obtained.

(2) *Ammonia Assay*

The assay was based on the method of Park and Fenton (1973) using an ammonia sensitive electrode (EIL model 80002-2, with Celgard 2400 microporous polypropylene membranes).

For plasma ammonia assays in anæsthetized animals 2.5 ml of blood were withdrawn from a cannulated carotid artery. Samples of blood were also removed from the jugular vein in five normal conscious cats (Hovell, O'Reilly, Calder and Povey, 1970) to assess the effect of anæsthesia. The samples were placed in heparinized tubes and spun down; the plasma was then decanted for analysis. Samples of cerebrospinal fluid (CSF) were taken from the cisterna magna of anæsthetized animals using a 25 G needle passed through the atlanto-occipital membrane. About 1 ml could be obtained at any one time.

The sample was pumped at 1.2 ml/min through the ammonia probe where it was mixed with 0.15 mol/l sodium hydroxide pumped at 0.6 ml/min resulting in a final pH of about 11. This short interval ($\simeq$ [illegible] s) between alkalinization and assay makes hydrolysis of glutamine insignificant (*see* Proeiss and Wright, 1973). Between samples about 2 ml of 0.15 mol/l saline containing 10 μmol/l ammonium chloride was pumped through the probe. This protocol was automated using an adapted Technicon autoanalyser proportioning pump and sampler. Standard solutions of ammonium chloride (25 to 1600 μmol/l) made up in 0.15 mol/l saline at pH 7 were interleaved with samples for calibration purposes. The saline used for making up all solutions was rendered ammonia-free by alkalinization and boiling. The probe potential, which was proportional to the logarithm of ammonia concentration down to sample concentrations of 50 μmol/l and deviated only slightly at 25 μmol/l, was plotted automatically on a Servoscribe pen writer. It should be noted that this method assays total ammonia (Amm.). At physiological pH most of this will be in the form of ammonium ion. The assay was very reproducible when used for CSF, but plasma slowly caused a reduction in the response to interleaved standard ammonia solutions. Precipitation of plasma proteins with perchloric acid prevents membrane contamination and avoids this problem (Moses, Thibert and Draisey, 1978).

(3) *Elevation of Blood and Brain Ammonia*

Ammonia was elevated by intravenous infusion of ammonium acetate solution. This salt was chosen because the solution is neutral.

The experiments of Lux and Loracher (1970) suggested that the reversal potential for postsynaptic inhibition of cat motoneurons would take about four minutes to reach a new equilibrium value after an instantaneous change in the local ammonia concentration. It was thus necessary to devise a protocol which was able to rapidly elevate blood ammonia and then keep it constant for *at least* four minutes in order to allow for any further delay of ammonia passing from blood to nervous tissue. To this end a brief investigation of ammonia clearance from the blood was undertaken in rabbits.

Rabbits were anæsthetized with i.v. urethane (25 per cent urethane with 10 mg/ml of pentobarbitone). A quantity of ammonium acetate solution (0.5 mol/l) was rapidly injected into an ear vein. At various times later samples of blood were removed from a cannulated carotid artery and the plasma ammonia was assayed. The result from a typical experiment is illustrated (fig. 1). In all the experiments plasma ammonia elevation was found to decrease exponentially after the injection of up to 1 mmol/kg of ammonium acetate with a time constant in the range 5 to 9 min. This result shows that ammonia clearance from the blood proceeds at a rate proportional to the elevation above the normal value. Furthermore, extrapolation back to zero time gives an intercept on the plasma ammonia axis corresponding approximately with the dose injected if it is assumed to distribute uniformly throughout the body. The same conclusions can be drawn from the experiments on rats of Rosado, Flores, Mora and Soberon (1962). Exponential analysis of their published data gives a mean time constant for ammonia clearance of 5.7 min (range 3.2 to 7.9). A similar conclusion has been formed from experiments on man (Lockwood, McDonald, Reiman, Gelbard, Laughlin, Duffy and Plum, 1979).

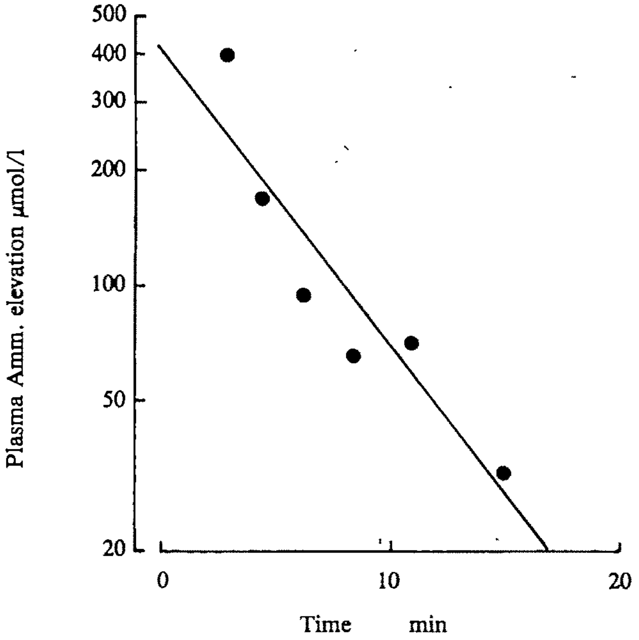

FIG. 1. Ammonia clearance from the blood of an anæsthetized rabbit. At zero time 500 μmol/kg of ammonium acetate was injected intravenously. Blood samples were taken and analysed at later times and the ammonia elevation above baseline (35 μmol/l) plotted against time. The solid line is a time constant of 5.5 min fitted by the method of least squares.

It can be predicted from these results that a 'step' change in blood ammonia should be produced by a rapid infusion of ammonium acetate followed by continuous infusion at the appropriate rate. This was generally found to be the case (fig. 2) although plasma ammonia showed some tendency to increase further after about 15 min of continuous infusion and the initial injection could not be made too rapidly without prejudice to the blood pressure. Empirically the best results were obtained with initial infusion of ammonium acetate at up to 300 μmol/kg/min followed by steady infusion at up to 150 μmol/kg/min for as long as elevated ammonia was required. A 1 mol/l solution of ammonium acetate was used to minimize the volumes injected and the infusions were controlled by a Palmer Ltd. 12 speed continuous slow injector.

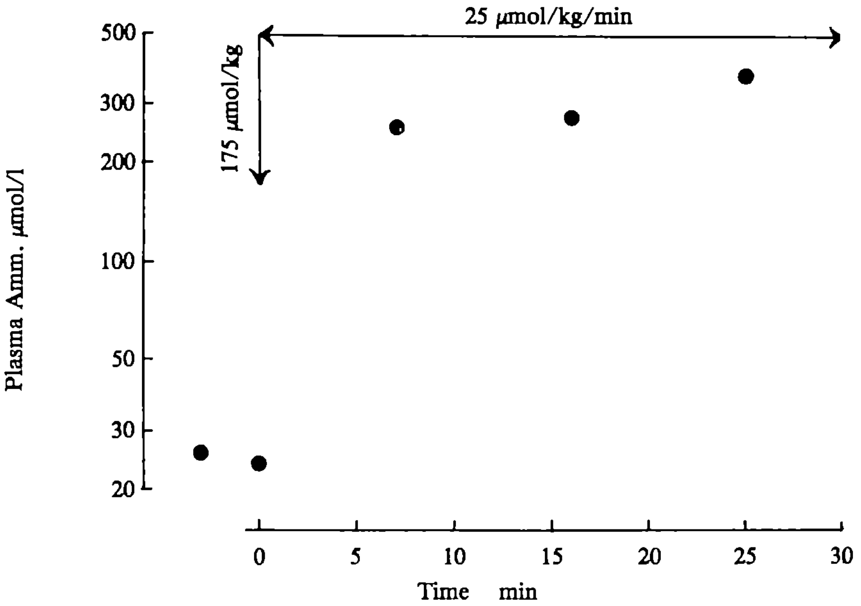

FIG. 2. Effect of ammonium acetate injection on plasma ammonia in an anæsthetized cat. Prior to the injection, plasma ammonia was 23-25 μmol/l (2 estimates 9 hrs apart). 175 μmol/kg of ammonium acetate was rapidly injected i.v. followed by continuous infusion at 25 μmol/kg/min. Blood samples were taken at the times indicated on the abscissa. A logarithmic scale was chosen for the ordinate to match the scale for ammonia concentration in the abscissa of fig. 5.

It should be noted that it was not necessary to predict exactly what ammonia levels would be reached by the injection protocol because these were actually measured during the electrophysiological experiments. It was sufficient to know that the levels were unlikely to be changing rapidly.

In three cats we made five comparisons of the plasma pH before and after ammonia elevation into the range where effects on inhibition were found. The changes in pH never exceeded 0.05 units and were not statistically significant ($P = 0.47$, randomization test for matched pairs: Siegel, 1956). Other authors have also concluded that no significant changes in systemic pH are produced by ammonium acetate injections provided that convulsions do not ensue (Hindfeldt and Siesjo, 1971*a*; Hawkins, Miller, Nielsen and Veech, 1973; Raabe and Gumnit, 1975; Koyuncuoğlu, Meyer, Şimşek and Sağduyu, 1978).

RESULTS

The aim of these experiments was to study postsynaptic inhibition in single motoneurons at both 'normal' and at least one elevated concentration of ammonia in the central nervous system. This required stable intracellular records of long duration. The strength of the hyperpolarizing component of inhibition was estimated from the amount of transmembrane current required to reverse the ipsp. The values at different ammonia levels were normalized by that measured at 'normal' ammonia, thus permitting data from different cells to be combined. This procedure differs slightly from that of Lux (1971) who measured the deviation of the ipsp reversal *potential* from the resting potential. The two methods are equivalent if, as we show below, motoneuron input resistance is not changed by ammonia. We have preferred to use reversal current rather than try to measure reversal potentials because this avoids errors due to microelectrode polarization when current is passed. The relationship between normalized reversal current and deviation of reversal potential from the resting potential will, however, be somewhat non-linear if the motoneuron membrane exhibits rectification over this voltage range.

(1) *Selection of Records for Analysis*

A total of 23 microelectrode experiments were performed and 59 posterior biceps-semitendinosus motoneurons were studied in detail. From these a total of 33 cells were selected on the criteria of being held for at least 15 min with membrane potentials of -70 mV or greater when measurements of input resistance (R_{in}) or ipsp reversal current (I_{rev}) were made. Fifteen of these cells were used to study inhibition at elevated ammonia concentrations. The remaining 18 were not held long enough to study the effects of ammonia and have been retained as a control sample. Sometimes, during intravenous infusion of ammonium acetate we observed a transient fall in blood pressure (up to 20 mm Hg) which often led to loss of the intracellular position of the microelectrode.

(2) *Motoneuron Input Resistance*

Input resistance of the 18 control motoneurons and of 12 cells also studied at elevated ammonia concentrations were plotted in histogram form in fig. 3 (the three cells without R_{in} measurements were all studied at ammonia levels sufficient to totally block inhibitory hyperpolarization; there was no need to check the constancy of R_{in} in these cases). There is no suggestion from this histogram that the population of motoneurons on which ammonia effects were studied is very different from the controls.

In 9 motoneurons, R_{in} was measured several times at both 'normal' ammonia levels and during elevation of blood ammonia into the range where inhibition was affected. The ratio of the mean input resistance measured at normal and elevated ammonia is plotted for these cells in fig. 4. There is no consistent effect of ammonia on R_{in} (the populations before and after ammonia infusion are not significantly

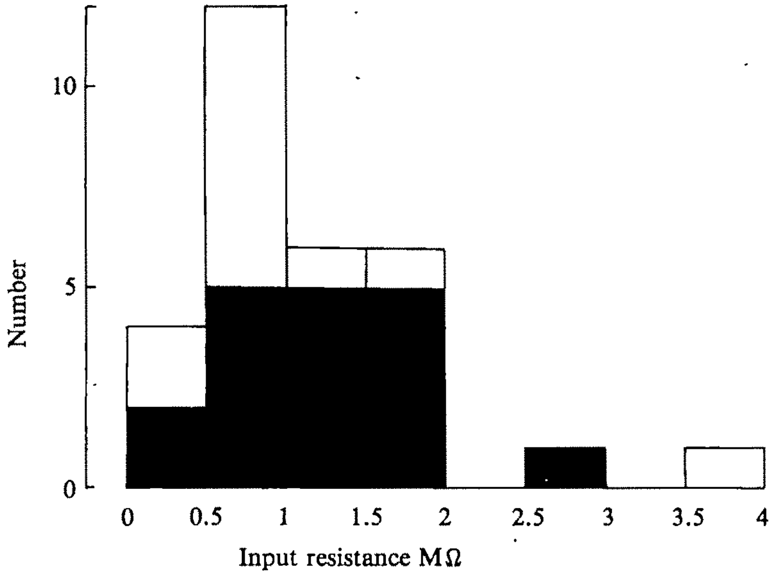

FIG. 3. Distribution of input resistance measurements in the sample of motoneurons selected for detailed analysis. Solid blocks: control cells; open blocks: cells also studied at elevated ammonia concentrations. (The values measured at 'normal' ammonia levels are plotted.)

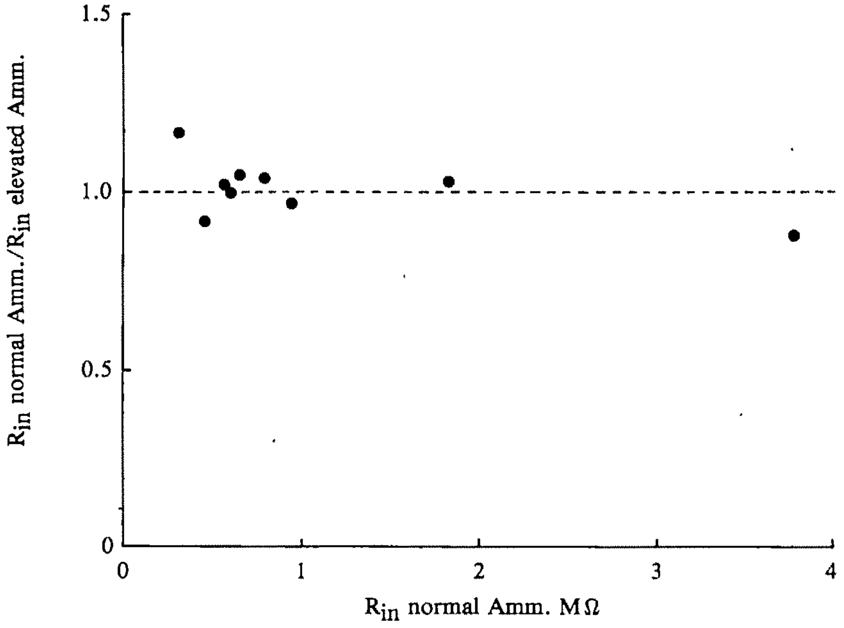

FIG. 4. The lack of effect of elevated ammonia on motoneuron input resistance. The ratio of R_{in} measured before and after ammonia elevation has been plotted against the value at the normal ammonia level. The ratio is not significantly different from one.

different on the Wilcoxon matched-pairs signed ranks test: Siegel, 1956). This is in agreement with the conclusions of Lux (1971). When R_{in} was measured with different amounts of polarizing current many of the motoneurons showed some degree of anomalous rectification (Nelson and Frank, 1967). To give an extreme example, one cell had an input resistance of 0.53 ± 0.03 MΩ (mean ±SD, $n = 5$) measured with a hyperpolarizing current of 5 nA, and 0.79 ± 0.20 ($n = 6$) when measured at 2 nA. In order to avoid this complication, comparisons have always been made between R_{in} measurements at comparable current values.

(3) *Effect of Elevated Ammonia on Postsynaptic Inhibition*

Fifteen cells conforming to the selection criteria were held long enough (18 to 164 minutes) to study the effects of ammonia elevation.

The procedure used in most cases was to penetrate a biceps-semitendinosus motoneuron and wait until membrane potential and input resistance stabilized. The (hyperpolarizing) current required to just reverse the Ia ipsp (evoked by stimulating the nerve to the antagonist, quadriceps) was then estimated, usually several times. The range of currents required in different cells was between 6 and 36 nA. Ammonia infusion was then started. If the recording was maintained with minimal change in membrane potential and input resistance, then the ipsp reversal current stabilized to

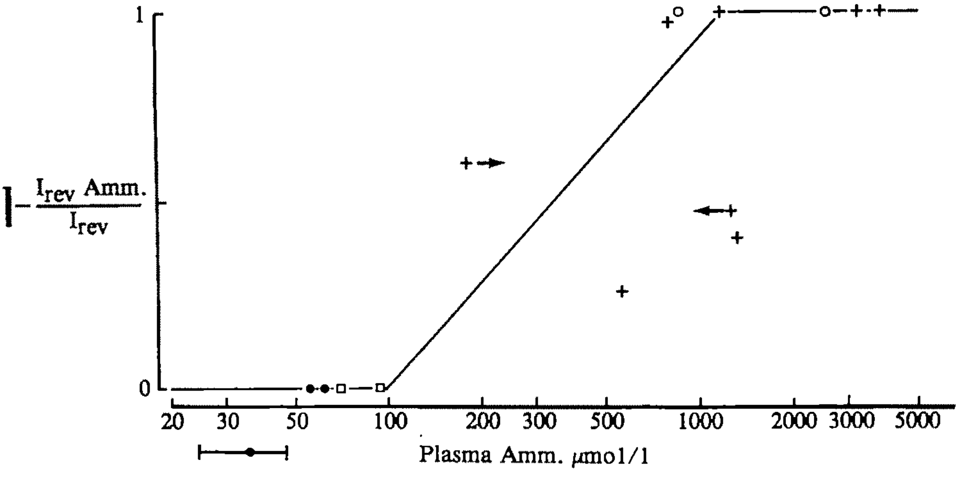

FIG. 5. Effect of plasma ammonia concentration on inhibitory hyperpolarization. The estimate of inhibitory hyperpolarization in terms of the ratio of reversal currents before and after ammonia elevation is plotted on the ordinate. Complete abolition of inhibitory hyperpolarization has the value of one. Plasma ammonia concentration is plotted on a logarithmic scale. Points where only a single value was obtained from one motoneuron are plotted as crosses. The other symbols refer to cells which were each studied at two elevated ammonia concentrations. The cross with an arrow pointing to the right is from an experiment in which the ammonia infusion was turned off before the plasma sample was taken. The cross with an arrow pointing to the left refers to an experiment in which the infusion rate had just been increased and for which the plasma ammonia concentration was likely to have been out of equilibrium with the CSF. There is considerable scatter of the data for ammonia values between 100 and 2000 μmol/l. The continuous line drawn through these points is taken from fig. 6 but shifted along the abscissa to take into account the steady state ammonia distribution across the blood brain barrier. The normal range of plasma ammonia concentration in the cat is indicated below the abscissa.

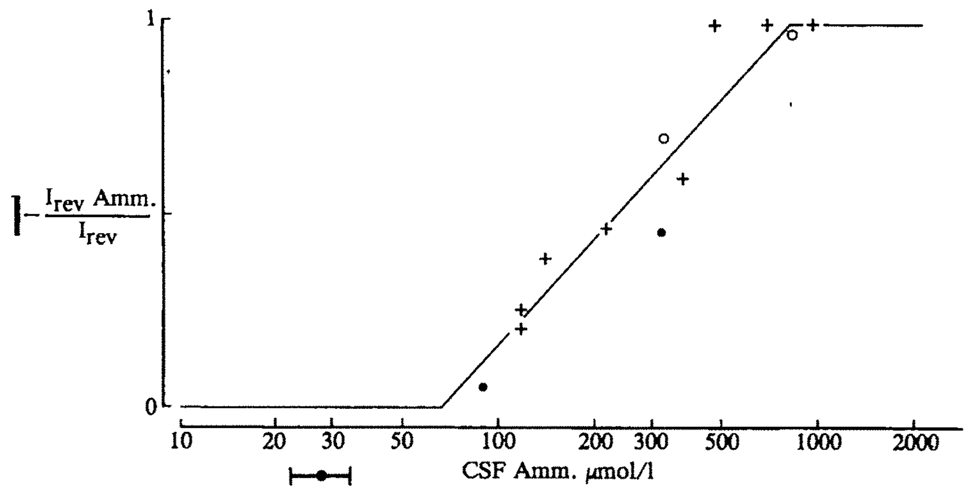

FIG. 6. Effect of CSF ammonia concentration on inhibitory hyperpolarization. The conventions are the same as in fig. 5. The sloping line has been fitted by the method of least squares as an empirical description of the data. The normal range of CSF ammonia concentration in anæsthetized cats is indicated below the abscissa.

a new (lower) value 10 to 20 minutes after the start of infusion. A sample of blood or CSF was then taken to correspond with the reversal current estimate. The effect on inhibition was then defined as one minus the ratio of the reversal current at elevated ammonia to that at the normal level. This procedure of normalization permitted us to accumulate data from several cells. This was necessary since only on five occasions did we succeed in holding a cell long enough to obtain data at two steady elevated ammonia concentrations.

Sometimes the first cell was lost during ammonia infusion and a second one found soon after. In these cases we attempted to continue ammonia infusion until the reversal current fell to zero (complete absence of inhibitory hyperpolarization). In these cells there was no need for a measure of reversal current at normal ammonia for normalization or of any check on the constancy of input resistance.

In the earlier experiments of the series plasma ammonia was analysed. It was clear from data accumulated from several animals that plasma ammonia levels of up to 100 μmol/l had no detectable effect on inhibition, whereas values in excess of 2000 μmol/l were always associated with the complete loss of inhibitory hyperpolarization (fig. 5). The effects of intermediate values of plasma ammonia were, however, very variable. This was not altogether unexpected since there must be some diffusional delay for ammonia passing from the blood to the vicinity of the motoneurons. Since CSF may approximate more closely the composition of the neuronal extracellular space, we assayed samples of cisternal CSF in later experiments. A continuous relation was found between the reduction in inhibitory hyperpolarization and CSF ammonia concentration (fig. 6). The effect of ammonia was apparent at a concentration of less than 100 μmol/l and saturated at about

800 μmol/l. Half reduction in the current required to reverse the ipsp occurred at 230 μmol/l. The sets of data on plasma and CSF ammonia effects are consistent when account is taken of the fact that in the steady state ammonia distributes across the blood brain barrier in such a way that the CSF concentration is about two-thirds of the plasma concentration (Schwab and Dammaschke, 1962; Moore, Strohmeyer and Chalmers, 1963; Müting, Heinze, Reikowski, Betzien, Schwarz and Schmidt, 1968; Dutton, Harris and Davies, 1974; Hindfeldt, 1975*a*, *b*; Hunt and Otis, 1975).

In these experimental cats we assumed that the plasma and CSF ammonia levels would be 'normal' if either no ammonium acetate had been infused or at least one hour had elapsed since an injection. This was done to avoid taking too many blood samples which otherwise prejudiced the blood pressure, despite volume replacement with dextran. The quantity of CSF was also limited. A range of control values for ammonia was therefore obtained by analysing samples from cats prepared for other experiments.

Arterial plasma ammonia was estimated in 20 samples from 12 animals of which 10 were anæsthetized (7 with pentobarbitone, 2 with α-chloralose, 1 with halothane) and 2 were high spinal unanæsthetized after induction with halothane. A value of 34.1 ± 8.2 μmol/l (mean ± SD) was obtained. A value of 136 μmol/l from another spinal animal judged to have been moribund has not been included in the sample. Seven blood samples were also taken from the jugular vein in 5 normal conscious cats. These gave an ammonia value of 38.9 ± 17.3 μmol/l. There is clearly no very strong effect of anæsthesia and surgery, and the value for the combined data of 'normal' plasma ammonia (35.4 ± 11.1) has been indicated below the abscissa on fig. 5. Seven samples of CSF from 6 anæsthetized cats (3 with pentobarbitone, 3 with halothane) gave a 'normal' value of 28 ± 5.9 μmol/l which has been indicated on fig. 6.

(4) *Levels of Ammonia Necessary to Induce Convulsions*

In some animals we observed convulsions during the course of ammonia administration, despite the fact that they were deeply anæsthetized (these convulsions were not precipitated by a fall in blood pressure). Since it might be expected that the levels of ammonia needed to induce fits in unanæsthetized animals would be smaller, the measurements that we have made are of value in suggesting an *upper* limit for the extracellular ammonia concentration.

In 2 preparations isolated twitches were observed at CSF ammonia levels of 273 and 319 μmol/l. In 3 other animals more sustained convulsions were noted at levels of 874, 937, 1220 and 1378 μmol/l. These levels are sufficient to largely or completely abolish the hyperpolarization of postsynaptic inhibition (*see above*).

In one animal we obtained two separate measures of the *blood* ammonia concentration associated with convulsions. When ammonia infusion was maintained at a very rapid rate (480 μmol/kg/min) the animal started to convulse after about six minutes, at which time the blood ammonia had reached 1650 μmol/l. Following a recovery period a much slower infusion was started (80 μmol/kg/min).

The animal then gave convulsive jerks after more than twenty minutes of infusion, at a blood ammonia level of 1050 μmol/l. This result suggests that a rapid infusion regime will tend to overestimate the blood ammonia levels required to induce convulsions, presumably because there are delays in diffusion of ammonia into the central nervous system and in its action on the neurons themselves.

DISCUSSION

We undertook this study with the primary aim of assessing the role of ammonia in convulsive disorders. Although it has long been known that administration of ammonia induces convulsions and that even physiological activity can lead to an increase in brain ammonia (*see* Tsukada, 1966), in recent reviews its role as an endogenous convulsant agent is commonly dismissed. For example, McIlwain and Bachelard (1971, p. 197) remark that 'unless factors of specific localisation are involved such mediation is unlikely'.

In this discussion we consider first the experimental data we have obtained and then assess whether the action on inhibition is likely to be the main way by which ammonia produces convulsions.

1. *The Dose-Response Curve for the Effect of Ammonia on Inhibitory Hyperpolarization*

The data presented in figs. 5 and 6 suggest that ammonia reduces inhibitory hyperpolarization in a range of concentrations in the neuronal extracellular environment from less than 100 to about 800 μmol/l (for saturation). The current necessary to reverse the ipsp could be measured accurately provided no large changes in membrane potential occurred. The ammonia assay was also reproducible. It is possible, however, that in some experiments insufficient time was allowed for the reversal current to reach a new equilibrium value or that the ammonia concentration near the neuron was still changing. Since in all but one instance the reversal currents were measured at normal ammonia values before the measurements at elevated values, these errors will lead to overestimates of the ammonia concentrations necessary to affect inhibition. It was also noted that ammonium acetate infusion regularly caused a slight and reversible depolarization of the motoneuron (*see also* Lux *et al.*, 1970) which tended to counteract any decrease in the reversal current produced at low ammonia levels. It is possible, therefore, that the 'foot' of the dose-response curve extends to lower levels of ammonia than is suggested by fig. 6 and that smaller increases from the 'normal' value may have some effect. Nevertheless, the dose-response curve we have obtained for the relationship with CSF ammonia shows so little scatter that we feel it is fairly precisely defined. It follows that there must be a good correlation between cisternal CSF ammonia concentration and the concentration in the extracellular space surrounding spinal motoneurons. Lux and his colleagues have already presented evidence that the mechanism by which hyperpolarization is blocked involves an increase of ammonia in the extracellular space rather than intracellularly. Lux and Loracher (1970) attempted to estimate the effective dose range by injecting ammonium ions electrophoretically from an extracellular microelectrode near a motoneuron from which the intracellular recording was made. They assumed the distance over which the ammonium ions diffused and calculated a dose range from about 100 to 1000 μmol/l, which is in close agreement with our results (but a higher estimate is given by Lux *et al.*, 1970).

Ammonia has also been found to block the hyperpolarizing component of inhibition in other parts of the mammalian CNS: cerebral cortex (Raabe and Gumnit, 1975) and trochlear motoneurons (Llinás *et al.*, 1974). In both cases the infusion regimes followed were similar to those introduced by Lux *et al.* (1970). We would therefore suggest that similar levels of extracellular ammonia block the hyperpolarization in these cells as in the spinal motoneuron. On the other hand, when Allen, Eccles, Nicoll, Oshima and Rubia (1977) followed this infusion regime, they failed to abolish the hyperpolarization in hippocampal pyramidal cells, suggesting that the mechanism of this postsynaptic inhibition may be different.

In other species ammonia has been found to block hyperpolarizing inhibition. Nicoll (1978) showed such an effect in the frog spinal cord with an ammonia concentration of 600 μmol/l. In the crayfish stretch receptor higher doses are required (Meyer and Lux, 1974) and ammonia may be acting by a different mechanism (Hino, 1979; Deisz and Lux, 1980).

One notable feature of the dose response curve we have obtained is that it is very steep compared to that expected for a simple unimolecular reaction. This problem is explored in the Appendix.

2. *Brain Extracellular Ammonia Levels Found in Disease*

Chronic systemic hyperammonæmia is found in several pathological states with proven or suspected metabolic basis (*see* Hsia, 1974), and more generally in liver disease (Table 1). In selecting the data to illustrate in Table 1, we have chosen the highest levels of ammonia found (for example, after a protein meal) and have preferred more recent accounts, or those including analyses of CSF rather than just of plasma ammonia (though in most of these conditions with chronic ammonia elevation the steady state distribution of ammonia between plasma and CSF can probably be assumed (*see* Results)).

In all these conditions brain extracellular ammonia can be elevated into that range which we have shown reduces inhibitory hyperpolarization. Thus to the extent that our experiments with the cat motoneuron using acute ammonia administration are a good model for inhibition in the human nervous system with chronically elevated ammonia, we must conclude that inhibition will be compromised in these diseases. Loracher and Lux (1974) have shown that hyperpolarizing postsynaptic inhibition in cat motoneurons is reduced during insulin-induced hypoglycæmia, at a time when cerebral ammonia levels are known to be increased (Agardh, Folbergrova and Siesjo, 1978).

All these conditions are characterized by neurological symptoms. However, before one can proceed further with a wider assessment of the role of ammonia in the genesis of neurological symptoms it is necessary to consider other actions of ammonia and its relation to metabolism of the brain.

TABLE 1

Condition	*Authors*	*Plasma Amm. μmol/l*	*CSF Amm. μmol/l*
Ornithine transcarbamylase deficiency	Bruton, Corsellis and Russell, 1970	857	386
	Levin, 1971	706	318
	Sunshine, Lindenbaum, Levy and Freeman, 1972	730	
	Campbell, Rosenberg, Snodgrass and Nuzum, 1973	711	
Hyperarginæmia	Terheggen, Schwenk, Lowenthal, Van Sande and Colombo, 1970	479	358
	Levin, 1971	395	302
Arginosuccinic aciduria	Moser, Efron, Brown, Diamond and Neumann, 1967	166	174
	Levin, 1971	500	67
Citrullinuria	Mohyuddin, Rathbun and McMurray, 1967	471	177
Lysine intolerance	Colombo, 1971	400	114
	Simell, Perheentupa, Rapola, Visakorpi and Eskelin, 1975	560	
Propionicacidæmia	Landes, Avery, Walker and Hsia, 1972	176	
Methylmalonic aciduria	Kang, Snodgrass and Gerald, 1972	806	
Reye's syndrome	Glasgow, Cotton and Dhiensiri, 1972	1490	
	Aoki and Lambroso, 1973	796	
	Haller, 1975	529	
	Snodgrass and Delong, 1976	557	
Cirrhosis	Warren, Iber, Dolle and Sherlock, 1960	214	107
	Caesar, 1962	223	129
	Lockwood *et al.*, 1979	62-264	
Cirrhotic coma	Warren *et al.*, 1960	643	429
Cerebral atrophic syndrome	Rett and Stöckl, 1968	114	

3. *Other Actions of Extracellular Ammonia*

In this study we have accepted the suggestion of Lux and his colleagues that the major way in which ammonia produces convulsions is by blocking the hyperpolarizing component of some postsynaptic inhibitory processes. Our incidental observations that convulsive activity could be produced in anæsthetized animals when the concentration of ammonia in the CSF was in the range where inhibitory hyperpolarization would be nearly, or completely, eliminated is certainly in accord with this idea. One of the difficulties in assessing this hypothesis more carefully is that ammonia has a variety of direct and indirect effects on nervous tissue. Furthermore, ammonia has both excitant and depressant actions on the nervous system as a whole and it is clear from descriptions of animal and human behaviour during its administration (Owen, Tyor, Flanagan and Berry, 1960; Eichler, 1964; Cohn and Castell, 1966; Hindfelt and Siesjo, 1971*a*; Cole, Rutherford and Owen Smith, 1972) that these effects develop at similar doses and with no clear distinction in their timing.

It is likely that the multiplicity of effects of ammonia is partly the result of having different actions intracellularly from those that it produces when acting extracellularly. The factors governing the distribution of ammonia between intracellular and extracellular compartments are still obscure (*see below*). In this section we will only discuss those other actions of ammonia which may result when the extracellular concentration is of the order of 1000 μmol/l or less.

Neuronal depolarization. In agreement with Lux we often observed small but maintained depolarizations ($\simeq$ 5 mV) of motoneurons following ammonia administration. They did not seem to be attributable to movement of the microelectrode. The mechanism of depolarization may be twofold. There is evidence that some nerve cell membranes are permeable to ammonium ions in the resting state, probably through the channels that confer permeability to potassium (*see* Hille, 1973). An increase in extracellular ammonia will thus depolarize the cell directly and also lead to displacement of intracellular potassium to the extracellular space (*see* Hawkins *et al.*, 1973, and Benjamin *et al.*, 1978, for evidence of an increase in extracellular potassium). Rises in extracellular potassium, with their attendant neuronal depolarization, have often been considered to play a part in convulsive disorders (*see* Prince, 1978).

It is unlikely, however, that this could be the primary mechanism of ammonia-induced convulsions because the maximum increase in extracellular potassium would be of the same order as the increase in ammonium ion concentration, that is, about 1000 μmol/l. Nevertheless, any depolarization produced would be expected to enhance neuronal excitability.

Ammonia may lead to neuronal depolarization by less direct mechanisms, particularly in unanæsthetized animals. Two examples would be the removal of tonic inhibition, and disinhibition of neurons which supply synaptic excitation.

Change in intracellular pH. Experiments on snail neurons (Thomas, 1974) and on the squid giant axon (Boron and De Weer, 1976) have shown that extracellular ammonia can produce a rapid rise in intracellular pH. This is explained by an influx of NH_3 which then forms ammonium ion, thus depleting the cell interior of hydrogen ions. Thomas's data shows that about 2000 μmol/l external ammonia at pH 7.4 (corresponding to the pH of *cat* CSF) is needed to increase the internal pH of the snail neuron by 0.1 unit. Whole cat brain has a similar buffering power to the snail neuron (Roos, 1965; Thomas, 1974) so that, unless there are large differences in the buffering power of individual cells (or parts of cells) in the brain, the extracellular ammonia concentrations which affect postsynaptic inhibition in the cat will produce only small changes in intracellular pH.

Changes in intracellular pH can also be induced by altering the extracellular carbon dioxide concentration. In four animals we deliberately hyperventilated with air while monitoring the reversal current for inhibition in a motoneuron. Although this procedure should (qualitatively) produce the same increase in internal pH as ammonia administration, we found no effect on the magnitude of the reversal current. Nor was there any change when ventilation was continued with a mixture of 5 per cent carbon dioxide in oxygen. It is therefore unlikely that the action of ammonia on postsynaptic inhibition is mediated by changes in intracellular pH. Intravenous ammonium acetate infusion does not alter the pH of CSF itself in the preconclusive stage (Hindfelt and Siesjo, 1971*a*). It is possible, however, that changes in intracellular pH are responsible for some of the phenomena described in the next section.

Presynaptic inhibition. Sverdlov and Ruchinskaya (1977*a*, *b*) reported that doses of ammonium acetate which suppress postsynaptic inhibition of monosynaptic reflexes in the cat spinal cord also reduce primary afferent depolarization when monitored as the dorsal root potential. They therefore proposed that ammonium salts might have their convulsant action by the joint depression of both presynaptic and postsynaptic inhibitions. Iles, Jack and Lewis (1979), however, have shown that the methods used to assess presynaptic inhibition by these workers could give misleading results. The action of ammonia on presynaptic inhibition and its relevance to convulsions is still unclear.

Conduction block. Block of afferent nerve fibres has been reported by Lux *et al.* (1970). Conduction failure could result from an increase in intracellular ammonia because these authors showed that ammonia injection into motoneurons caused a reduction in action potential amplitude.

Thus, there is still very limited understanding of the actions of ammonia, especially with respect to its depressant effects. Although it seems reasonable to assume that the main convulsant action is by reduction of postsynaptic inhibitory hyperpolarization, a significant contribution from depression of presynaptic inhibition cannot be ruled out. Direct depolarization, accompanied by an elevation of extracellular potassium ions, may also make a small contribution.

4. *Brain Ammonia Metabolism*

It is well known that the brain can produce ammonia as a result of a variety of biochemical processes. When studied in tissue slices the net ammonia production by brain can be very large. McIlwain and Bachelard (1971) quote a figure of more than 100 μmol/kg wet weight/s. In other words, if this rise took place in the extracellular space in parallel with the rise intracellularly, ammonia could increase to a level which started to jeopardise hyperpolarizing inhibition in less than a second.

One important uncertainty here is our poor understanding of the distribution of ammonia between and within brain cells. In a variety of species, including the cat, total brain ammonia is approximately 300 μmol/kg (and therefore more than 300 μmol/l in intracellular fluids). In CSF the ammonia concentration is about 30 μmol/l. If ammonia only existed in the ionic form NH_4^+ this result would not be surprising. It is the distribution expected for an ion passively distributed between intracellular and extracellular compartments when account is taken of the resting potential of the nerve cell. However, both the intracellular and extracellular pH of the brain is of the order of 7.0 to 7.4 (Roos, 1965) and in this range up to 2 per cent of ammonia occurs in the uncharged form, NH_3. According to the studies of Robin, Travis, Bromberg, Forkner and Tyler (1959), NH_3 crosses cell membranes with even greater ease than carbon dioxide. NH_3 should thus be equally distributed across the nerve cell membrane. Therefore, if there were no difference between intracellular and extracellular pH the cytosolic and extracellular NH_4^+ concentrations would also be the same. A pH difference of 0.5 units would still only lead to an approximately three-fold difference in concentration, whereas the observed difference is at least ten-fold. Hindfelt (1975*a*) has shown that the difference persists even when the CSF concentration is as much as ten times normal. Thus it would appear that cells in the brain have the capacity of actively accumulating ammonia. This seems to be a property common to many cells; for example there is a seventy-fold ratio between intracellular and extracellular concentrations for the liver (*see* Brosnan, 1976, for a review).

Part of the explanation for the large difference between intracellular and extracellular concentrations may lie in an unequal distribution of ammonia within the cell. Various workers have found that isolated mitochondrial fractions of cells are relatively rich in ammonia compared with the total cell content (Robin, Vester, Wilson and Andrus, 1960; Harris and Bassett, 1971; Sainsbury, 1978). Sainsbury has suggested that the most plausible interpretation of her data is that a substantial proportion of the intracellular ammonia exists in a fixed or bound form (*see also* Chow and Pond, 1972).

The importance of drawing attention to this uncertainty about the nature of intracellular ammonia is the relevance to the interpretation of total brain ammonia measurements made during preconvulsive, convulsive and comatose states, particularly when ammonia is produced endogenously in the brain. As shown in this paper, ammonia blocks the hyperpolarizing component of postsynaptic inhibition when the extracellular level rises above three times the normal level, and has maximal effect at about thirty times normal. Without an exact understanding of the factors setting the distribution between extracellular and intracellular compartments it is not possible to assess satisfactorily the meaning of a rise of total brain ammonia.

The factor of 'specific localisation' mentioned by McIlwain and Bachelard (*see above*) may thus not only include differences in concentration in different parts of the brain, but also the differences in various compartments within one region of the brain.

5. *Involvement of Ammonia in Epilepsy*

To clearly demonstrate that ammonia is involved in the initiation or promotion of seizures it would be necessary to monitor brain extracellular ammonia concentration in the preconvulsive state. There is at present no satisfactory method for doing this.

However, ammonia is intimately associated with amino acid metabolism in the brain, and there have been an increasing number of suggestions that seizures may be associated with biochemical disturbances in brain tissue, involving amino acid transmitters (*see* Emson, 1978). This evidence comes mainly from animal studies with artificially induced epilepsies, but there is also data from samples of human epileptogenic tissue (Tursky, Lassanova, Sramka and Nadvornik, 1976; further references may be obtained from Iles and Hamilton, 1976). One particular case concerns the neurotransmitter GABA (Meldrum, 1975; Wood, 1975), whose synthesis in synaptic terminals involves the release of ammonia from glutamine.

Wood and Peesker (1974) developed an equation describing the effectiveness of the GABA system in producing synaptic inhibition, which they presumed to be reciprocally related to the tendency for seizures to occur. The equation incorporates not only the brain concentration of GABA, but, more importantly, the relative activity of the enzyme glutamic acid decarboxylase which converts glutamate to GABA. If this enzyme is inhibited (as in vitamin B_6 deficiency), the normal sequence of reactions in synaptic terminals synthesizing GABA will be partly arrested at the stage after glutamine is deaminated to glutamate by glutaminase. Thus both glutamate and ammonia would tend to rise in these terminals. Glutamate is likely to be trapped inside whereas ammonia (as NH_3) would diffuse into the extracellular space and increase the concentration there.

In keeping with this view it has been observed that some of the convulsant procedures which Wood mentions as exemplifying his hypothesis increase brain ammonia. For example, hyperbaric oxygen poisoning causes seizures and the susceptibility to convulsions correlates well with the rate of decrease in brain GABA. Banister, Bhakthan and Singh (1976) have observed that brain ammonia is elevated by this procedure and ascribe the convulsions to this factor. Clearly both mechanisms may contribute to the seizure tendency and it will be a difficult problem to resolve their relative importance.

Another example concerns hydrazine, which is known to inhibit glutamic acid decarboxylase. Wood (1975) has used data from animals treated with different doses of hydrazine as evidence in favour of his equation. If a reduction in synaptic synthesis and thus release of GABA were the sole cause of hydrazine induced convulsions, then one can expect that the only detectable electrophysiological effect would be a suppression of pre- and postsynaptic inhibition mediated by GABA. Liebl (1975) and J. F. Iles, J. J. B. Jack and G. H. Lewis (unpublished) have indeed found a small (15 per cent) reduction of the dorsal root potential (an indirect sign of presynaptic inhibition) in the cat spinal cord after administration of hydrazine. However, Liebl also found a substantial depression of hyperpolarizing postsynaptic inhibition resulting from a depolarizing shift in the ipsp reversal potential of spinal motoneurons. This synaptic pathway is not thought to be GABA mediated and, besides, the mechanism of action is, of course, precisely that produced by a rise in brain ammonia.

Some contribution of ammonia to epileptic disorders seems therefore a possibility, but it may be a daunting technical task to obtain definitive evidence.

SUMMARY

When ammonia is administered in large doses to mammals it causes convulsions and coma. In smaller doses it may produce signs both of increased and decreased excitability in the nervous system.

(1) Lux *et al.* (1970) suggested that the increase in excitability, including convulsions, is primarily attributable to an increase in the concentration of ammonia in the neuronal *extracellular* space, leading to a depression of the hyperpolarizing component of some types of postsynaptic inhibition. We show experimentally in this paper that the threshold for this effect is at about three times the normal extracellular ammonia concentration, with a maximal effect (complete abolition of inhibitory hyperpolarization) at levels about thirty times normal.

(2) These levels of extracellular ammonia are reached in several human pathological conditions characterized by neurological disturbance.

(3) Other factors which may contribute to the convulsant action of ammonia are discussed.

(4) The mechanism for depressed neuronal excitability induced by ammonia is uncertain. It may involve block of action potential conduction in nerve axons.

(5) The distribution of ammonia between intracellular and extracellular compartments in both brain and other tissues is poorly understood. Cells appear to have the capacity to accumulate ammonia to concentrations well above that found in the extracellular space. Further analysis of the physiological and pathological roles of ammonia in the brain will undoubtedly require an analysis of the factors governing the distribution of ammonia between the various compartments.

(6) It is possible that seizures resulting from a disturbance in the brain biochemistry of the amino acid transmitters (such as GABA) will be promoted by consequent increases in extracellular ammonia.

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APPENDIX

The Mechanism of Action of Ammonia

Lux (1971) concluded that postsynaptic inhibition at the motoneuron is predominantly mediated by an increase in permeability to chloride ions (*cf.* Sypert and Bidgood, 1977). The reversal potential for an ipsp thus follows the chloride equilibrium potential, E_{Cl}. This potential is normally negative to the resting potential implying the presence of an outwardly directed chloride pump extruding chloride ions from the cell against a passive inward leak. Lux explained the action of ammonia as a block of this pump leading to passive distribution of chloride and the loss of inhibitory hyperpolarization. Ammonia appeared to act from the outside of the neuron but whether as ammonium ion or in the uncharged form is not clear. Related compounds such as some amino acids (Lux and Schubert, 1969) and hydrazine (Liebl, 1975) have similar actions.

It is possible to predict from the Lux hypothesis what dose-response relation should be measured in the present experiments. We have assumed that with the chloride pump fully active in a cell with a resting potential of -75 mV E_{Cl} is -95 mV. This corresponds to intracellular and extracellular chloride concentrations of 3.46 and 140 mmol/l. With the chloride pump fully blocked E_{Cl} moves to the resting potential and the internal chloride concentration is 7.55 mmol/l. The magnitude of the inward chloride leak will depend upon the deviation of internal chloride from 7.55 mmol/l. Both the constant field equation and a constant conductance formulation give an almost linear relation between leak current and internal chloride over the range $3.46 \leqslant \text{Cl} \leqslant 7.55$ mmol/l. We have therefore simply chosen convenient mathematical descriptions such as linear, parabolic or square law dependence on internal chloride. The chloride pump current will also be a function of internal chloride. We have examined linear, hyperbolic and square law relations. The inhibition of the chloride pump by ammonia has been modelled by a unimolecular reaction with Michaelis constant *K*. For any given degree of pump inhibition the internal chloride [Cl] will reach a value where the pump and leak currents are equal. For example, with a linear pump and linear leak, and assuming a linear current-voltage relation for the motoneuron:

$$\text{let } \alpha = \frac{\text{internal [Cl] with pump blocked, i.e. Amm.} \rightarrow \infty}{\text{internal [Cl] with pump fully active, i.e. Amm.} = 0}$$

$$\text{then } 1 - \frac{{}^{\text{Irev}}\text{Amm.}}{\text{Irev}} = 1 - \left\{ \ln\left(\frac{\text{Amm.}}{k+\text{Amm.}}[1-\alpha]+\alpha\right) \Big/ \ln \alpha \right\}$$

The same solution is given by a square law pump with a parabolic leak and other combinations can be obtained very simply.

The model predicts a sigmoidal relation between the normalized reversal current for the ipsp and the logarithm of ammonia concentration, which extends over more than two log units of concentration. The observed relation (fig. 6) is much steeper, though some uncertainty remains over the extent of the foot of the curve (*see* Results). The predictions of the model are very insensitive to the form of the dependence of leak and pump currents on internal chloride and only slightly altered by a current-voltage relation with rectification. In passing it may also be remarked that the ammonia concentration at which the reversal current is half maximal is not always equal to the Michaelis constant for the action of ammonia on the pump. The experimentally determined steep relation between normalized reversal current and ammonia concentration could be explained by some 'co-operativity' in the action of ammonia on the pump or may imply that the mechanism of action is different to that proposed above. It has been shown using ion sensitive electrodes that ammonia elevation does lead to an increase in chloride concentration within cat motoneurons, but the absolute values reached are not reliably defined by this technique (Lux, 1974).

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CLINICAL, PATHOLOGICAL, HLA ANTIGEN AND IMMUNOLOGICAL EVIDENCE FOR DISEASE HETEROGENEITY IN MYASTHENIA GRAVIS

by D. A. S. COMPSTON, A. VINCENT, J. NEWSOM-DAVIS *and* J. R. BATCHELOR

(*From the National Hospital for Nervous Diseases, Queen Square, the Department of Neurological Science, Royal Free Hospital and Royal Postgraduate Medical School, Hammersmith Hospital, London*)

INTRODUCTION

THE weakness and fatiguability of skeletal muscle in myasthenia gravis (MG) is thought to be due to interference with neuromuscular transmission that follows binding of antibody to acetylcholine receptors (AChRs). Anti-AChR antibody is present in 85 to 90 per cent of patients with generalized MG (Mittag, Kornfeld, Tormay and Woo, 1976; Lindstrom, Seybold, Lennon, Whittingham and Duane, 1976). MG immunoglobulin can passively transfer MG to the mouse (Toyka, Drachman, Griffin, Pestronk, Winkelstein, Fischbeck and Kao, 1977) and anti-AChR antibody is present in infants with neonatal MG through placental transfer from myasthenic mothers (Keesey, Lindstrom, Cokely and Hermann, 1977). Plasma exchange, which lowers serum antibody, is associated with clinical remission (Pinching, Peters and Newsom-Davis, 1976) and reveals an inverse relation between muscle strength and serum antibody levels (Dau, Lindstrom, Cassel, Denys, Shev and Spitter, 1977; Newsom-Davis, Pinching, Vincent and Wilson, 1978). The number of functioning AChRs is reduced in MG (Fambrough, Drachman and Satyamurti, 1973) and the reduction is adequate to account for the physiological abnormalities (Ito, Miledi, Vincent and Newsom-Davis, 1978). The antibody appears to exert its effect by several mechanisms including complement mediated lysis of the post-synaptic membrane (Engel, Lambert and Howard, 1977), increased rate of degradation of acetylcholine receptor (Stanley and Drachman, 1978) and possibly by direct pharmacological block (Shibuya, Kazutake and Nakazawa, 1978).

The mechanism underlying the breakdown in tolerance to AChR that leads to the

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Abbreviations: Myasthenia gravis = MG, Acetylcholine receptors = AChRs, Histocompatibility leucocyte system = HLA. ^{125}I-alpha bungarotoxin = αBuTx. HLA-D related workshop = HLA-DRw.

production of anti-AChR antibody is unknown, but several features of the disease suggest that the mechanism may not be the same in all patients. For example, the thymus gland, which is now known to have important immunological functions and which has long been recognized as abnormal in this disease (Weigert, 1901), shows striking differences in its pathology (Castleman and Norris, 1949), and these differences relate to the age of onset of the disease, sex incidence, and outcome of thymectomy (Simpson, 1958).

The human histocompatibility leucocyte system (HLA) consists of several genetic loci (HLA-A, B, C and D) which are closely placed on the 6th chromosome. Each locus is multiallelic so that there are a number of alternative gene forms which may be found at each locus in any individual. The genes on each chromosome are collectively known as a haplotype. The gene products are detected by cellular and serological techniques and are expressed on cell surfaces. Genes determining immune response to synthetic and viral antigens (IR genes) map to the I region of the murine histocompatibility system (which is called H-2). The products of certain I region genes (Ia antigens) are detected serologically on the surface of B lymphocytes, macrophages, subsets of T lymphocytes, sperm and endothelial cells. The human Ia analogues are HLA-DRw antigens. The evidence suggests that Ia antigens are involved in co-operation between macrophages and T helper cells which enable B lymphocytes to respond to T cell-dependent antigens and amplify the generation of cytotoxic T lymphocytes. These same gene products may be involved at later stages in immune response and in the action of suppressor cells. In contrast HLA-A, B and C antigens are likely to be involved in recognition of target cells by cytotoxic T lymphocytes. In population studies some HLA-A, B, C, D and DRw antigens occur together in individuals more often than would be expected from a knowledge of their individual frequencies (linkage disequilibrium).

The association of certain HLA antigens with subpopulations of MG patients, in particular that between young female patients and HLA-B8 (Pirskanen, 1976), and between older patients and HLA-A3 (Fritze, Herrman, Naeim, Smith and Walford, 1974) has led investigators to suggest that there might be two forms of the disease, and provides further support for the belief that there may be more than one mechanism underlying the disease. HLA-DRw antigens are of particular interest in diseases where there is independent evidence for the involvement of immune processes, since these gene products are the closest markers at present detectable of those HLA genes which are thought to be involved in regulating the immune response.

In this study, we have typed for HLA-A, B, C and DRw antigens in a group of MG patients in whom the disease was clinically and immunologically well defined. The analysis of associations found to exist between clinical, pathological and immunological characteristics supports the view that more than one mechanism may underlie the breakdown in tolerance to AChR and the production of anti-AChR antibody.

CLINICAL MATERIAL

The 68 patients with myasthenia gravis whom we studied were attending either the National Hospital for Nervous Diseases, Queen Square, or the Royal Free Hospital. All were Caucasians. The diagnosis of MG was based on typical symptoms and signs of the disease, and responsiveness to intravenous edrophonium (Tensilon).

Sera from 50 control patients were studied. In this group were 10 healthy subjects, 8 patients with rheumatoid arthritis, 22 patients with neurological disease which might have had an immune basis and 10 patients with other (non-immune) neurological disorders.

METHODS

Muscle Extracts

Human calf muscle was obtained at amputations and either extracted within a few hours or stored frozen at −20° C. The muscle was trimmed of tendon and fascia, chopped and homogenized in 0.1 M phosphate buffer pH 7.4. The homogenate was centrifuged at 20,000 g for thirty minutes and the pellet resuspended in an equal volume of 0.02 M phosphate buffer made 1 per cent in Triton X-100 (B.D.H.). After two hours at room temperature it was centrifuged at 20,000 g for one hour. The supernatant extract was filtered and stored at 4° C. All solutions contained 0.02 per cent sodium azide and 0.1 mM phenyl-methyl sulphonyl fluoride to inhibit bacterial growth and proteolytic activity.

Estimation of the Number of αBuTx Binding Sites in Muscle Extracts

The extracts were labelled with ^{125}I-alpha bungarotoxin (αBuTx) (2-5 nmolar) and the amount of bound αBuTx determined by filtration through DEAE discs (Whatman DE 81) as previously described (Newsom-Davis *et al.*, 1978). Control incubations were performed using muscle extract which has been pre-treated with an excess (20-fold) of non-radioactive bungarotoxin before addition of the radioactive toxin. The number of binding sites for αBuTx ranged between 0.5 and 2 picomoles/ml of extract (representing approximately 1 to 4 pmol/g of starting material).

Anti-AChR Antibody Assay

Muscle extracts were labelled with ^{125}I-αBuTx and 0.1 picomol of αBuTx binding sites (50 to 200 μl of muscle extract) were incubated at room temperature with 0.25 to 5.0 μl of the patient's serum. After two hours an excess (25 to 100 μl) of antihuman IgG was added (Seward Laboratories). After leaving overnight at 4° C the tubes were centrifuged for two minutes at 10,000 r.p.m. and the pellet washed three times in 20 mM phosphate buffer with 0.1 per cent Triton X-100. The tubes were counted for 20 to 50 seconds in a Mini instrument gamma ray counter (efficiency 70 per cent). The counts precipitated in the presence of extract which had been pre-incubated with non-radioactive αBuTx were subtracted. The results are expressed as nmol of αBuTx binding sites precipitated per litre of serum. 50 sera from control patients and normal subjects were assayed using 5 μl of serum.

Comparison between Normal and Extraocular Anti-AChR Titres

Muscle from an amputated limb was stored at −20° C. Extraocular muscle from several subjects was taken post mortem and stored at −20° C until use. Extraction of both types of muscle was done within twenty-four hours of each other. The number of binding sites for αBuTx was 1 pmol/ml in each case. Sera were assayed against the two extracts simultaneously.

Inhibition of αBuTx Binding to Muscle Extract by MG Sera

Inhibition of αBuTx binding was determined at equilibrium by pre-incubating 0.1 pmol of muscle extract with 20 to 50 μl of MG sera followed by addition of 2 nmol αBuTx. After overnight incubation the number of binding sites labelled with the radioactive toxin was determined by the DEAE method. Sera which produced more than 50 per cent inhibition of ^{125}I-αBuTx binding to the muscle AChR (relative to control sera) were repeated at lower concentration.

Auto-antibodies and Striated Muscle Antibody

Anti-striated muscle antibody was assayed by indirect immunofluorescence on longitudinal and transverse section of rat skeletal and cardiac muscle, using serum diluted 1 in 10.

HLA Typing

HLA typing was done as previously described (Compston, Batchelor, Earl and McDonald, 1978), using well validated antisera in a complement mediated cytotoxicity test on unfractionated lymphocytes for the assignment of HLA-A, B and C antigens and an enriched population of B lymphocytes for the DRw antigens. Antisera used for determining HLA-DRw antigens were either those used (and where necessary donated by other laboratories) for the original assignment of DRw antigens in the 7th International Histocompatibility workshop (1977) or were standardized against these antisera. Positive typing for any antigen was based on concordant reactions with two or more antisera and where the results were equivocal typing was repeated either on the same or a fresh sample.

Statistics

The data were analysed by the University of London CDC 6600 computer. One-way analysis of variance, student's t-test and the χ^2 test were used. The probability value and standard deviation for each statistic were computed. In the text, the F, t and χ^2 statistics are quoted with the number of degrees of freedom appropriate to the data written as a subscript. Mean values are followed by their standard deviation. In any study where multiple comparisons are being made statistically significant results may arise by chance. We have not applied any statistical corrections for this possibility.

RESULTS

Sixty-eight unrelated patients were studied, in whom the age of onset ranged from 5 to 76 years. Cases with congenital myasthenia were excluded since this form of the disease is likely to have a different ætiology (Vincent and Newsom-Davis, 1979*a*). There were 38 males (55.9 per cent) and 30 females (44.1 per cent) (Table 1). The distribution of the clinical grade (Osserman and Genkins, 1971) for the patients as a whole was similar to previous reported studies: 6 cases were ocular (Grade 1, 9 per cent), 21 were mild generalized cases (Grade 2A, 31 per cent), 17 had moderate generalized disease (Grade 2B, 25 per cent), 9 were acute severe (Grade 3, 13 per cent) and 15 late severe (Grade 4, 22 per cent) (Table 1).

TABLE 1. CLINICAL GRADE IN 68 PATIENTS WITH MYASTHENIA GRAVIS

		*Clinical stage at peak of illness**				
	Total	1	2A	2B	3	4
Male	38 (55.9%)	5	9	12	4	8
Female	30 (44.1%)	1	12	5	5	7
Total	68	6 (9%)	21 (31%)	17 (25%)	9 (13%)	15 (22%)

* Osserman and Genkins, 1971.

TABLE 2. THYMUS PATHOLOGY IN 68 PATIENTS WITH MYASTHENIA GRAVIS

		Percentage	
	No.	*of total*	*of thymectomized patients*
Thymectomy			
thymoma	13	19.1	31
non-tumourous	29	42.6	69
No thymectomy	24	35.3	—
Thymic pathology not available	2	2.5	—

Thymus Pathology

Forty-two patients had had a thymectomy. Thirteen (31 per cent) had a thymoma (Table 2). The remaining 29 (69 per cent) had non-tumourous pathological changes (hyperplasia or involution) or normal thymic histology. Two patients who had had a thymectomy at other hospitals were not included in the analyses of pathology because the results were not available. In the absence of radiological evidence of thymoma the 24 unoperated cases were included in the non-tumourous group. The age of onset in non-tumour cases showed a bimodal distribution with peaks at 10–30 and 60–70 years (fig. 1). Bimodality was also evident for males considered

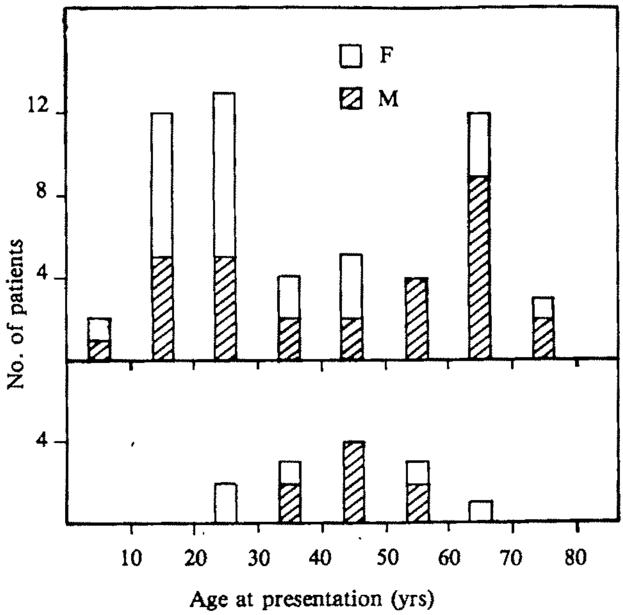

FIG. 1. Distribution of patients according to their sex and age at presentation. *Upper panel*, non-thymomatous cases; *lower panel*, thymoma cases.

separately. Taking 40 years of age as an arbitrary division in the non-tumour cases, there was a significant association between presentation at less than 40 years and females and conversely, between presentation at more than 40 years of age and males ($\chi_1^2 = 4.56$, $P = 0.03$. Table 3). The modal value for thymoma cases lay between the two peaks for the non-tumour cases (fig. 1). There was no association between sex and the presence of thymoma, and no correlation between thymic pathology and severity of illness at peak (not shown in Tables).

TABLE 3. AGE AT PRESENTATION AND SEX IN 68 PATIENTS WITH MYASTHENIA GRAVIS

			Non-tumourous histology	
	No.	*Thymoma*	*Aged < 40*	*Aged > 40*
Male	38 (55.9%)	8 (62%)	13 (42%)	17 (71%)
Female	30 (44.1%)	5 (38%)	18 (58%)	7 (29%)
Total	68	13	31	24

$\chi_1^2 = 4.56$
$P = 0.03$.

Anti-striated Muscle Antibody

Striated muscle antibody was found in 31/68 (45 per cent) patients (Table 4). There was a significant association between the presence of striated muscle antibody and thymoma, the antibody being present in 12/13 (92 per cent) patients with thymoma compared to 8/29 (27 per cent) patients with non-tumourous histology ($\chi_1^2 = 15.07$, $P = 0.00009$) and 18/53 (34 per cent) patients without thymoma in the whole study ($\chi_1^2 = 14.33$, $P = 0.0001$) (Table 4). The frequency of striated muscle antibody in the patients without thymoma aged less than 40 was 6/29 (21 per cent) and in the older group 12/24 (50 per cent) (Table 4).

TABLE 4. STRIATED MUSCLE ANTIBODY IN 68 PATIENTS WITH MYASTHENIA GRAVIS

		Thymoma					
					Negative/not tested		
Striated muscle antibody	*Total*	*Not known*	*Negative*	*Positive*	*All patients*	*Under 40 yrs*	*Over 40 yrs*
Positive	31 (45.6%)	1	8 (27.6%)	12 (92%)	18 (34%)	6 (21%)	12 (50%)
Negative	37 (54.4%)	1	21 (72.4%)	1 (8%)	35 (60%)	23 (79%)	12 (50%)
Total	68	2	29	13	53	29	24

$\underbrace{29 \quad 13}_{\chi_1^2 = 15.07,\ P = 0.00009}$ $\underbrace{13 \quad 53}_{\chi_1^2 = 14.33,\ P = 0.0001}$

Other Immune Diseases

Other immune diseases were present in 14/68 (20 per cent) patients. These included thyroid disease, diabetes of juvenile onset, rheumatoid arthritis, Sjögren's syndrome, subacute combined degeneration, temporal arteritis, and polymyalgia rheumatica. Three out of 13 (23 per cent) patients with thymoma had other immune diseases compared to 3/31 (10 per cent) patients without thymoma presenting under the age of 40 years and 8/24 (33 per cent) older patients without thymoma. The difference in frequency of other immune diseases between the younger and older patients without thymoma was significant ($\chi_1^2 = 4.73$, $P = (0.03)$ (Table 5). There was no sex difference in the frequency of other immune diseases (8/14, 57.1 per cent males; 6/14, 42.8 per cent females; not shown in Table). The 3 younger patients with other immune diseases were all female and in the older group 3 were female and 8 were male. The severity of disease at the peak of illness was not associated with age of onset, sex or the presence of other immune diseases.

TABLE 5. ASSOCIATED IMMUNE DISEASES IN 68 PATIENTS WITH MYASTHENIA GRAVIS

			Non-tumourous histology	
	Total	*Thymoma*	*Under 40 yrs*	*Over 40 yrs*
Associated immune disease	14 (20%)	3 (23%)	3 (10%)	8 (33%)
No associated immune disease	54 (80%)	10 (77%)	28 (90%)	16 (67%)
All patients	68	13	31	24
			$\chi_1^2 = 4.73$	

Anti-(Human Limb) AChR Antibody and Clinical State

Anti-AChR antibody as determined by immunoprecipitation of ^{125}I-αBuTx-labelled AChR from human muscle extracts ranged between −0.2 and +0.17 nmol/l in 50 control patients with a mean value of 0.008±0.1 nmol/l after subtraction of control blanks. The results of the individual control groups with disease did not differ materially from that of the healthy group (fig. 2). On the basis of these studies antibody titres greater than 0.19 nmol/l were regarded as abnormal (fig. 2). Elevated titres were found in 63/68 (93 per cent) patients in samples taken on entry into the study, which was not necessarily at the peak of illness (fig. 3). Of the 5 exceptions, 3 were ocular cases at the time of sampling, 2 of whom had had mild generalized disease while the other had always been an ocular case. Of the remaining 2 cases, one was in spontaneous remission following acute severe disease and the other had mild generalized disease.

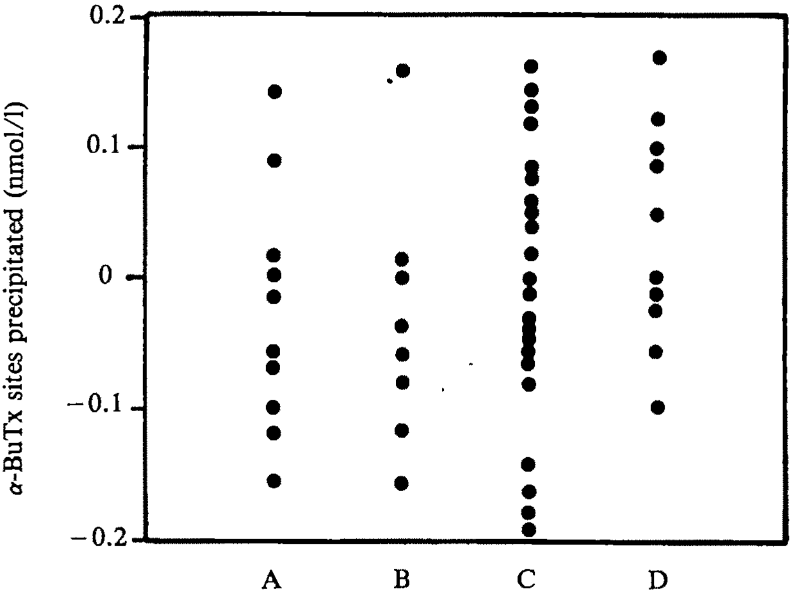

FIG. 2. Anti-AChR antibody in 4 groups of control patients. A, normal healthy individuals. B, patients with rheumatoid arthritis. C, patients with neurological disease (immune disorders). D, neurological disease (non-immune disorders). The results are given as ^{125}I-αBuTx binding sites precipitated after subtraction of control blanks (*see* Methods).

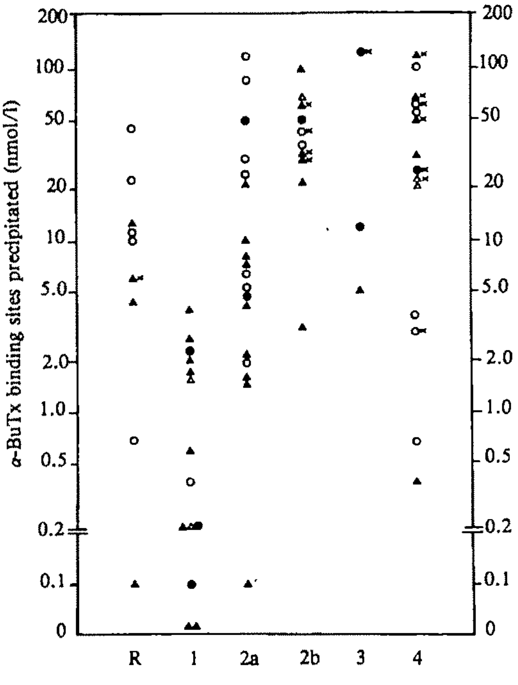

FIG. 3. Anti-AChR antibody in 6 groups of MG patients. R = remission. 1 = ocular involvement only. 2a = mild generalized disease. 2b = moderate generalized disease. 3 = acute severe disease. 4 = chronic severe disease. Triangles, males; circles, females; open symbols, less than 40 years at age of onset; closed symbols, over 40 years at age of onset. x = marks thymoma cases.

Wide variation was seen in the antibody titre within each grade (*see* fig. 3, Table 6). Patients with symptoms confined to the eyes (Grade 1) showed lower titres than other groups including those in remission. The grade of disease at the time of blood sampling had a significant influence on the mean titre of AChR antibody ($F_{6,61}$ = 3.54, $P = 0.004$) (Table 6).

TABLE 6. COMPARISON OF ANTIBODY LEVELS TO LIMB AND OCULAR ACETYLCHOLINE RECEPTOR

Clinical state at time of sampling	*No. of patients*	*Mean titre of Anti-AChR nmol/l (±SD)*		*Mean ratio limb/ocular*
		Limb	*Ocular*	*(±SD, No. of pts.)*
Remission	9	19.3 (19.7)	4.1 (5.2)	3.54 (3.01, 8)
Ocular	14	1.6 (2.1)	1.3 (1.5)	1.28 (0.57, 11)
2A	18	22.7 (35)	7.1 (10)	3.66 (2.7, 17)
2B	10	34.1 (22)	10.9 (7.5)	3.55 (2.2, 10)
3	3	45.2 (65)	12.9 (18)	4.67 (3.0, 3)
4	14	40.9 (40)	23.3 (25)	2.32 (1.8, 13)
		$F_{6,61} = 3.54$ $P = 0.004$	$F_{6,61} = 3.29$ $P = 0.007$	$F_{6,61} = 2.60$ $P = 0.027$

Anti-(Human Limb) AChR Antibody and Histological Findings

A comparison was made between the titre of anti-(human limb) AChR and thymus histology (Table 7). The mean titre in the 13 patients in whom a thymoma was demonstrated was 50.92±38.67 nmol/l. Two patients had had a thymectomy but the histology was not available and they were excluded from this analysis. In the remaining 53 non-tumour cases (29 operated and 24 unoperated patients) the mean titre was 19.35±29.53 nmol/l and this difference was significant ($F_{1,61} = 10.53$, $P = 0.001$). The titre was 8.52±13.83 nmol/l in the 24 patients presenting at more than 40 years and 28.35±37.76 nmol/l in the 29 younger patients. The difference between these two groups and the patients with thymoma was significant ($F_{2,63} = 8.42$, $P = 0.0006$).

TABLE 7. MEAN TITRE OF ANTI-ACHR ANTIBODY IN PATIENTS WITH AND WITHOUT THYMOMA

			Patients without thymoma	
	All patients without thymoma	*Patients with thymoma*	*Aged over 40*	*Aged under 40*
Number studied	53	13	24	29
Mean titre of anti-AChR±SD	19.35±29.53	50.92±38.67	8.52±13.83	28.32±35.76
	$F_{1,64} = 10.53$ $P = 0.001$		$F_{2,63} = 8.42$ $P = 0.0006$	

Anti-(Human Ocular) AChR Antibody

Antibody binding to human ocular AChR was found in 63/67 (94 per cent) patients. Of the 4 patients in whom this antibody could not be detected, 2 had ocular disease, one had generalized disease, and one had late severe disease. Anti-(human limb) AChR was also not detected in these patients when assayed at the same time and under the same conditions (*see* Methods). Two patients who had low titres of ocular AChR antibody had no detectable limb AChR antibody. One of these was an ocular case.

As in the case of anti-(human limb) AChR the clinical grade significantly influenced the titre of anti-(human ocular) AChR ($F_{6,61} = 3.29$, $P = 0.007$) (Table 6) but high titres were not specifically associated with ocular disease. As previously reported (Vincent and Newsom-Davis, 1979*b*) the ratio of limb AChR antibody to ocular AChR antibody varied widely between individuals, ranging from 0.5 to 8.0. Although the clinical grade significantly influenced the ratio of limb to ocular antibody titres ($F_{6,61} = 2.60$, $P = 0.03$) (Table 6), the most striking finding was a low limb to ocular ratio in ocular cases suggesting a relatively higher production of ocular antibody in these cases. The overall mean ratio of limb to ocular AChR antibody was 2.11:1 in males and 3.53:1 in females ($F_{6,61} = 7.69$, $P = 0.007$; not shown in Tables).

Inhibition of αBuTx Binding to AChR

Inhibition of αBuTx binding to limb AChR by MG sera was very variable (*see* Vincent and Newsom-Davis, 1979*b*) and no significant correlations were demonstrated.

Other Auto-antibodies

Auto-antibodies other than AChR and striated muscle antibody were found in 40/68 (58.8 per cent) patients (Table 8). Two or more antibodies were found in 6/40 (15 per cent) patients (not shown in Table). Auto-antibodies were found in 18/38 (47.3 per cent) male patients and 22/30 (73.3 per cent) female patients ($\chi^2_1 = 4.66$, $P = 0.03$).

TABLE 8. PRESENCE OF AUTO-ANTIBODIES IN 68 PATIENTS WITH MYASTHENIA GRAVIS

	Auto-antibodies positive				
	Total	*Male*	*Female*	*Negative*	*All patients*
Thymoma	5 (38%)	2	3	8 (62%)	13
Under 40 yrs	18 (58%)	4	14	13 (42%)	31
Over 40 yrs	17 (71%)	12	5	7 (29%)	24
All Patients	40 (58.8%)	18	22	28 (41.2%)	68

$\underbrace{18 \qquad 22}$

$\chi^2_1 = 4.66$

$P = 0.03$

Five out of 13 (38 per cent) patients with thymoma had other auto-antibodies compared to 18/31 (58 per cent) patients without thymoma presenting before the age of 40 and 17/24 (71 per cent) older patients without thymoma. These differences were not significant (Table 8). Fourteen out of 18 (77 per cent) patients with other auto-antibodies in the younger age group were female and 12/17 (71 per cent) patients with auto-antibodies in the older group were male ($\chi_1^2 = 8.24$, $P = 0.004$). These figures probably simply reflect the sex distributions in the two age groups. There was no association between the presence of auto-antibodies and other auto-immune disease, age of onset, or the presence of thymoma.

HLA Antigen Frequencies

Selected HLA antigen frequencies are shown in Table 9. In the 68 patients, as a group, there was a significant increase in the frequency of HLA-B8 (patients 28/68, 41.2 per cent; controls 56/200, 28 per cent; $\chi_1^2 = 4.09$, $P = 0.04$) and a significant decrease in the frequency of HLA-DRw5 (patients 4/68, 5.9 per cent; controls 33/200, 17 per cent; $\chi_1^2 = 5.6$, $P = 0.02$).

TABLE 9. FREQUENCY OF HLA ANTIGENS IN 68 PATIENTS WITH MYASTHENIA GRAVIS

	Patients (*n = 68*)	*Controls* (*n = 200*)	χ_1^2	*P value*
A1	32 (47%)	73 (37%)	2.37	
A2	28 (41.2%)	99 (49.5%)	1.41	
A3	17 (25%)	52 (26%)	0.03	
B7	22 (32.4%)	47 (24%)	2.08	
B8	28 (41.2%)	56 (28%)	4.09	0.04
B12	18 (26.5%)	72 (36%)	2.02	
DRw1	7 (10.3%)	22 (11%)	0.03	
DRw2	21 (30.9%)	60 (30%)	0.01	
DRw3	26 (38.2%)	54 (27%)	3.06	
DRw4	24 (35.2%)	67 (34%)	0.07	
DRw5	4 (5.9%)	36 (18%)	5.86	0.02
DRw6	8 (11.8%)	33 (17%)	0.87	
DRw7	17 (25%)	59 (30%)	0.50	

HLA-A1 B8 DRw3 (Tables 10 and 11)

The mean age of onset in patients with HLA-B8 was 29.1 years compared to 46.5 in patients without this antigen ($t_{66} = 3.99$, $P = 0.0002$). This compared with figures of 34.4 and 43.8 years ($t_{66} = 2.03$, $P = 0.04$) in patients with or without HLA-A1 and 29.5 and 45.5 ($t_{66} = 3.56$, $P = 0.001$) in patients with or without DRw3, respectively.

There was an association between the presence of HLA-B8 and female patients; 17/28 (60.7 per cent) HLA-B8-positive patients were female compared to 13/40 (32.5 per cent) HLA-B8-negative patients ($\chi_1^2 = 4.23$, $P = 0.04$). No significant association was seen between sex and the presence of HLA-A1 or DRw3.

TABLE 10. CLINICAL AND PATHOLOGICAL ASSOCIATIONS WITH THE PRESENCE OF A1, B8, DRw3 IN 68 PATIENTS WITH MYASTHENIA GRAVIS

						Thymoma	
		Total	*Mean age at onset*	*Female*	*Male*	*Positive*	*Negative*
HLA-A1	Positive	32	34.4	18	14	3	18
	Negative	36	43.8	12	24	10	11
			$t_{66} = 2.03, P = 0.04$	$\chi_1^2 = 2.74, P = 0.10$		$\chi_1^2 = 4.01, P = 0.04$	
B8	Positive	28	29.1	17	11	2	19
	Negative	40	46.5	13	27	11	10
			$t_{66} = 3.99, P = 0.0002$	$\chi_1^2 = 4.23, P = 0.04$		$\chi_1^2 = 7.12, P = 0.007$	
DRw3	Positive	26	29.5	14	12	3	17
	Negative	42	45.5	16	26	10	12
			$t_{66} = 3.56, P = 0.001$	$\chi_1^2 = 1.04, P = 0.31$		$\chi_1^2 = 3.23, P = 0.07$	

TABLE 11. ANTIBODY LEVELS IN PATIENTS WITH DRw3

	DRw3 positive	*DRw3 negative*
Total	26	42
Striated muscle		
Positive	9 (35.6%)	22 (52.4%)
Negative	17 (65.4%)	20 (47.6%)
Acetylcholine receptor (limb) antibody (nmol/l)	21.63±27.87	27.01±36.51
Acetylcholine receptor (ocular) antibody (nmol/l)	5.44±14.39	11.84±18.45
Auto-antibodies		
Positive	17 (65%)	23 (54%)
Negative	9 (35%)	19 (46%)

The absence of thymoma was positively associated with the presence of HLA-B8, but only when the comparison was restricted to the thymectomized patients and unoperated cases were excluded. Nineteen out of 21 (90.5 per cent) thymectomized patients with HLA-B8 did not have a thymoma compared to 10/21 (47.6 per cent) patients without HLA-B8 ($\chi_1^2 = 7.12$, $P = 0.007$). The same trend was observed with HLA-A1 ($\chi_1^2 = 4.01$, $P = 0.04$) and DRw3 ($\chi_1^2 = 3.23$, $P = 0.07$) but the significance was less marked than for HLA-B8. However, this association may have been due to a selection artefact because thymectomy was usually carried out either in young patients in whom HLA-B8 was more frequent and thymoma less frequent, or in patients known to have thymoma who tended to be the older patients who have a lower frequency of HLA-B8.

For the patients as a whole, there was no association between the presence of HLA-A1, B8 or DRw3 and titres of limb or ocular acetylcholine receptor antibody, the presence of striated muscle antibody or of other auto-antibodies (*see* Table 11 for DRw3).

HLA-B12

There were 61 patients in whom both human limb and human ocular AChR antibody was detected when samples were tested under the same experimental conditions. The ratio of limb to ocular antibody levels in the 46/61 patients who were HLA-B12-negative was 3.30 and this compared with a ratio of 2.05 in the 15 patients who were positive for this antigen ($t_{61} = 3.06$, $P = 0.003$; not shown in Tables).

A3 B7 DRw2 (*Tables 12 and 13*)

The mean age of onset in patients with HLA-A3 was 52.0 years and 35.2 years in patients without this antigen ($t_{66} = 3.32$, $P = 0.001$) compared with mean age of 50.3 and 34.1 in patients with and without HLA-B7 ($t_{66} = 3.47$, $P = 0.001$) and 46.0 and 36.4 in patients with and without HLA-DRw2 ($t_{66} = 1.92$, $P = 0.06$), respectively (Table 12).

The presence of A3 was associated with male patients (14/38 HLA-A3-positive patients were male compared to 3/30 HLA-A3-positive female patients; $\chi^2_1 = 5.09$, $P = 0.02$), but this association was not seen with HLA-B7 or DRw2. No associations were seen between the presence of thymoma and HLA-A3, B7 or DRw2 (Table 12).

TABLE 12. CLINICAL AND PATHOLOGICAL ASSOCIATIONS WITH HLA-A3, B7, DRw2 IN 68 PATIENTS WITH MYASTHENIA GRAVIS

						Thymoma	
		Total	*Mean age*	*Female*	*Male*	*Positive*	*Negative*
HLA-A3	Positive	17	52.0	3	14	4	5
	Negative	51	35.2	27	24	9	24
			$t_{66} = 3.32$, $P = 0.001$	$\chi^2_1 = 5.09$, $P = 0.02$		$\chi^2_1 = 0.33$, $P = 0.56$	
B7	Positive	22	50.3	6	16	5	5
	Negative	46	34.1	24	22	8	24
			$t_{66} = 3.47$, $P = 0.001$	$\chi^2_1 = 2.80$, $P = 0.09$		$\chi^2_1 = 1.21$, $P = 0.27$	
DRw2	Positive	21	46.0	7	14	4	7
	Negative	47	36.4	23	24	9	22
			$t_{66} = 1.92$, $P = 0.06$	$\chi^2_1 = 0.87$, $P = 0.35$		$\chi^2_1 = 0.005$, $P = 0.94$	

TABLE 13. ANTIBODY LEVELS IN PATIENTS WITH DRw2

	DRw2 positive	*DRw2 negative*
Total	21	47
Striated muscle		
Positive	15 (71.4%)	16 (34.0%)
Negative	6 (18.6%)	31 (66.0%)
	$\chi_1^2 = 6.47, P = 0.009$	
Acetylcholine receptor (limb) antibody	12.35 ± 15.80	30.58 ± 37.51
	$t_{66} = 2.82, P = 0.006$	
Acetylcholine receptor (ocular) antibody	4.37 ± 5.10	13.92 ± 19.47
	$t_{53} = 3.00, P 0.004$	
Autoantibodies		
Positive	9 (42.8%)	31 (65.9%)
Negative	12 (57.2%)	16 (34.1%)
	$\chi_1^2 = 3.20, P = 0.07$	

Fifteen out of 21 (71.4 per cent) patients with DRw2 were striated muscle antibody-positive compared with 16/47 (34.0 per cent) patients without this antigen ($\chi_1^2 = 6.74$, $P = 0.009$) (Table 13). The mean level of limb acetylcholine receptor antibody was 12.35 ± 15.80 in patients with DRw2 compared to 30.58 ± 7.51 in patients without this antigen ($t_{66} = 2.82$, $P = 0.006$) (Table 13).

The mean level of ocular acetylcholine receptor antibody was 4.37 ± 5.10 nmol/l in patients with DRw2 compared to 13.92 ± 19.47 nmol/l in patients without this antigen ($t_{53} = 3.00$, $P = 0.004$ (Table 13). The ratio of these two antibodies showed no correlation with DRw2.

There was a tendency for auto-antibodies other than acetylcholine receptor or striated muscle antibodies to occur less frequently in patients with HLA-DRw2 (9/21, 42.8 per cent) than in patients without this antigen (31/47, 65.9 per cent) but this difference did not quite reach significant levels ($\chi^2 = 3.20$, $P = 0.07$) (*see* Table 13).

Thymus Pathology, Anti-AChR Antibody and HLA Antigens

The anti-AChR titre in patients with thymoma was significantly higher than in non-tumour cases and there was a negative association between thymoma and HLA-B8 (*see above*). The analysis of antibody titre with the presence of HLA-B7, DRw2, B8 and DRw3 was therefore repeated after exclusion of the tumour cases (Table 14). The mean titre in 25 non-tumour cases with HLA-B8 was 29.82 ± 32.41 nmol/l compared with a mean titre of 11.13 ± 23.61 nmol/l in 30 HLA-B8-negative cases ($t_{53} = 2.47$, $P = 0.007$). The corresponding values in 22 non-tumour cases with HLA-DRw3 were 22.85±28.68 nmol/l and in 33 patients without this antigen, 17.48±29.83 nmol/l. This difference was not significant ($t_{53} = 0.66$, $P = 0.25$).

TABLE 14. MEAN TITRES OF ACETYLCHOLINE RECEPTOR ANTIBODY IN PATIENTS WITHOUT THYMOMA

		Mean titre	*No.*	*t*	*P*
HLA-B8	Positive	29.82±32.41	25	2.47	0.007
	Negative	11.13±23.61	30		
HLA-DRw3	Positive	22.85±28.68	22	0.66	0.25
	Negative	17.48±29.83	33		
HLA-B7	Positive	7.89±8.52	17	2.05	0.02
	Negative	24.87±33.52	38		
HLA-DRw2	Positive	9.08±10.10	17	1.83	0.03
	Negative	24.40±33.60	38		
HLA-B8	Positive	29.82±32.41	25	2.72	0.004
HLA-B7		7.89±8.52	17		
HLA-DRw3	Positive	22.85±28.68	22	1.89	0.04
HLA-DRw2		9.08±10.10	17		

The mean titre in 17 HLA-B7-positive non-tumour cases was 7.89±8.52 nmol/l compared with a mean titre of 24.87±33.52 nmol/l in 38 HLA-B7-negative cases ($t_{53} = 2.05$, $P = 0.02$). The corresponding values in 17 patients with, and 38 patients without, HLA-DRw2 were 9.08±10.10 nmol/l and 24.40±33.60 nmol/l, respectively ($t_{53} = 1.83$, $P = 0.03$).

If the mean titre in the 17 non-tumour cases with HLA-B7 (7.89±8.52 nmol/l) was compared with that in 25 non-tumour cases with HLA-B8 (29.82±32.41 nmol/l) the difference was highly significant ($t_{40} = 2.72$, $P = 0.004$). There was a similar but less significant difference between the mean titre in 17 non-tumour cases with HLA-DRw2 (9.08±10.10 nmol/l) and the titre in 22 non-tumour cases with HLA-DRw3 (22.85±28.68 nmol/l; $t_{37} = 1.89$, $P = 0.04$).

DISCUSSION

The analysis of seventeen clinical, pathological and immunological characteristics has allowed three groups of patients to be distinguished and has also shown that immunological reactivity was related to the presence of certain HLA antigens. Two preliminary points need to be made. First, studies of healthy and of diseased Caucasian populations have shown that the antigens HLA-A1 B8 and DRw3 are in linkage disequilibrium and the same applies, to a lesser extent, to the antigens A3 B7 and DRw2 (Bodmer and Bodmer, 1978). In the present study these two haplotypes were frequently observed but immunological reactivity has been correlated with the presence of the individual antigens, not the haplotypes. Secondly, most patients with MG have serum IgG that binds α-BuTx labelled human AChR extracted from amputated calf muscle (Mittag *et al.*, 1976; Lindstrom *et al.*, 1976). There is now ample evidence that anti-AChR antibody is heterogeneous in its ability to bind to different AChR preparations (Lindstrom, Campbell and Nave, 1978; Vincent and Newsom-Davis, 1979*b*), to inhibit α-BuTx binding to AChR, and in its subclass (Lefvert and Bergström, 1978; Vincent and Newsom-Davis, 1979*b*; A. Vincent, B. Lang and J. Newsom-Davis, unpublished). Antibody heterogeneity may in part account for the observed relationship between clinical state and antibody titre, since the site of the antigenic determinant on the AChR may influence the effects of antibody binding. Thus although in the present study the clinical grade had a statistically significant influence on antibody titre, we confirmed earlier observations (Lindstrom *et al.*, 1976) that disease severity does not correlate strongly with antibody titre.

The three groups of patients we have defined had the following characteristics: the first group (A) was identified by the presence of thymoma. No clear HLA antigen association was present. The age at presentation lay between that of the other two groups, and neither sex predominated. Striated muscle antibody was almost always present, and the mean titre of anti-AChR antibody was the highest of the three groups. The second group (B) was characterized by patients presenting under the age of 40 years who typically were female. There were associations with HLA-A1, B8 and/or DRw3. These patients tended to have other auto-antibodies (excluding anti-striated muscle antibody) but not to exhibit other immune disease. Titres of AChR antibody were on average lower than in the thymoma group but higher than in the third group. Group (C) was characterized by presentation over the age of 40 years. The patients tended to be male, and there were associations with HLA-A3, B7 and/or DRw2. Other auto-antibodies, including striated muscle antibody, and other immune diseases were associated. Titres of AChR antibody were lower than in the other two groups.

The duration of illness was somewhat shorter in the patients presenting over 40 years of age, but this was not responsible for the lower anti-AChR levels because for the patients as a whole there was no tendency for short duration of illness to be associated with low anti-AChR. The lower anti-AChR titre in group C may be related to the higher proportion of patients in this group falling into clinical grades I and II. Conversely, most of the thymomatous cases fall into grades III and IV (*see* fig. 3).

Some of the associations within each group did not reach statistical significance and this might be attributed to the small numbers in some categories. Conversely, some of the weaker statistical associations might not be confirmed in further studies since chance associations can occur where multiple comparisons are made. However, in no case were there conflicting associations within or between groups.

Other studies have already reported some of the associations described here. Patients with thymoma have a high incidence of anti-striated muscle antibody (Downes, Greenwood and Wray, 1966; Feltkamp, Van den Berg-Loonen, Nijenhuis, Engelfriet, Van Rossum, Van Loghem and Oosterhuis, 1974) and show high anti-AChR antibody titres (Smith, Hammarström, Möller, Lefvert and Matell, 1978). HLA associations in thymoma cases, often based on small numbers, have been conflicting, showing either no association (Naeim, Keesey, Herrmann, Lindstrom, Zeller and Walford, 1978), an association with A2 (Oosterhuis, Feltkamp, Van Rossum, Van den Berg-Loonen and Nijenhuis, 1976) or with A3 (Fritze *et al.*, 1974). Taken together, the data do not suggest a strong association between thymoma and the HLA system.

Several studies have pointed out the association between the presence of HLA-B8 (Pirskanen, 1976; Fritze *et al.*, 1974; Feltkamp *et al.*, 1974; Van den Berg-Loonen, Nijenhuis, Engelfriet, Feltkamp, Van Rossum and Oosterhuis, 1977) or its linked antigens A1 and LD8a/DRw3 (Kaakinen, Pirskanen and Tiilikainen, 1975; Möller, Hammarström, Smith and Matell, 1976; Christiansen, Houliston and Dawkins, 1978; Naeim *et al.*, 1978) and young female Caucasian patients, and Feltkamp *et al.* (1974) found that antistriated muscle antibody was significantly less common in this group.

Our Group C distinguishes patients presenting over the age of 40 years in whom thymoma was not evident. In 4 this had been confirmed at operation, and of the remainder, 11 had no anti-striated muscle antibody, which makes thymoma very unlikely. None of the remaining 9 patients had radiological evidence of thymoma but its presence could not, of course, be wholly excluded. Nevertheless, clear differences existed between this group and Group A (thymoma) cases, justifying their separation. First, Group C showed associations with HLA-A3, B7 and/or DRw2. Fritze *et al.* (1974) showed an association with A3 in males of this age group but did not exclude thymoma cases. Secondly, age of onset and sex incidence differed for the two groups. Thirdly, anti-AChR antibody titres showed a highly significant difference.

Previous studies have revealed other features that distinguish the three groups proposed here. Patients with thymoma show a significantly better response to immunosuppressive drug treatment than comparably ill non-tumour cases (Newsom-Davis, Wilson, Vincent and Ward, 1979). Thymic hyperplasia is significantly more common in HLA-B8-positive females with early age of onset (Fritze *et al.*, 1974), and the response to thymectomy is better in this group (Simpson, 1958). These additional features are included in Table 15 which lists the typical characteristics for the three groups proposed on the basis of the present study.

Consideration of those characteristics which take precedence over others within each group and the role of the genetically determined HLA antigens should help to elucidate the mechanism leading to development of MG. Analysis of immunological reactivity in a heterogeneous group of patients is, however, likely to be complex since conflicting influences on antibody titres may exist. In this study anti-AChR antibody titres were found to be higher in patients with thymoma, and these patients showed a negative association with HLA-B8. This pattern of association may explain why the expected positive association between high antibody titres and the presence of HLA-B8 and DRw3 was not seen in the patients as a whole. But after exclusion of patients with thymoma, a significant positive association emerged between HLA-B8 and high AChR antibody titres, and the same trend was apparent for HLA-DRw3. These differences became more significant when comparisons of anti-AChR antibody levels were made between HLA-B8 and B7 ($P = 0.004$) and between HLA-DRw3 and DRw2 ($P = 0.04$).

TABLE 15. TYPICAL CHARACTERISTICS OF PROPOSED CATEGORIES OF MYASTHENIA GRAVIS*

	A	*B*	*C*
		No thymoma	
Thymus pathology	*Thymoma*	*(Hyperplasia)*	*(?Involution)*
Age at onset		*Under 40 yrs*	*Over 40 yrs*
Sex incidence	M = F	F > M	M > F
HLA associations	None demonstrated	A1, B8, DRw3	A3, B7, DRw2
Anti-AChR titre	High	Intermediate	Low
Anti-striated muscle**	Very high	Low	Intermediate
Other auto-antibodies**	Low	Intermediate	High
Other immune disease**	Low	Very low	Low
Response to thymectomy	Poor	Good	—
Response to immunosuppressive drugs	Good	Less good	—

* Based on present study and review of literature. ** Relative incidence (20 per cent, very low; 20–40 per cent, low; 40–60 per cent, intermediate; 60–80 per cent, high; 80 per cent, very high).

Previous studies have identified young females as a separate group (*see above*). In our study the strength of the statistical associations with age of onset was greater than with sex. Although the factors that allow the disease to manifest in early adult life may therefore show greater expression in females, they are probably acting independently of sex. The evidence showing a strong association of HLA-A1, B8 and DRw3 in patients whose disease began in early adult life (Group B) has a parallel in other immune diseases characterized by the production of tissue-damaging auto-antibodies and by early onset (Bodmer, 1978). Similarly studies of patients with HLA-B8 associated diseases and of other individuals with this antigen have consistently shown that antibody production to a wide range of antigens is quantitatively greater in individuals with HLA-B8 or DRw3 than in those without these antigens (Galbraith, Eddleston, Williams, Webster, Pattison, Donniach, Kennedy and Batchelor, 1976; Batchelor and Morris, 1978; Eddleston and Williams, 1978; Morris, Vaughan, Irvine, McCallum, Gray, Campbell, Duncan and Farquhar, 1976; Cudworth, Gamble, White, Lendrum, Woodrow and Bloom, 1977; Panayi, Wooley and Batchelor, 1978, 1979).

Older male patients showed associations with HLA-A3 and B7. Although no association was observed with DRw2, this linked antigen was associated with other characteristics in Group C patients. Relatively few diseases (for example, multiple sclerosis, Goodpasture's syndrome, severe combined immunodeficiency and tuberculoid leprosy) have been associated with any of these linked antigens (Batchelor, Compston and McDonald, 1978; Rees, Peters, Compston and Batchelor, 1978; Rimm and Bertin, 1977; de Vries and van Rood, 1978) and similarities in the mechanisms producing tissue damage are not easily discernible, in contrast to the HLA-B8/DRw3-associated diseases. Certain direct and circumstantial observations in individuals with these antigens suggest that their presence may determine quantitatively low levels of antibody production (Panayi *et al.*, 1978; Eddleston and Williams, 1978; Morris *et al.*, 1976; de Vries and van Rood, 1978). We have found that antibody titres to limb and ocular AChR were significantly lower in patients with DRw2 when compared to patients without this antigen and there was a trend for auto-antibodies to be less common in these patients. These differences were found whether the patients were considered as a whole or after exclusion of thymoma cases. In this respect our results are consistent with the hypothesis that individuals with DRw2 or the products of closely linked genes synthesize antibody less readily than individuals without these antigens. However there are obvious exceptions to this, in particular, the association between anti-glomerular basement membrane antibody mediated Goodpasture's disease and HLA-DRw2, and in the present study the association between the presence of striated muscle antibody and HLA-DRw2.

The evidence for three relatively distinct groups of patients with MG, based on clinical and immunological features, has implications for the pathogenesis of the disease. One possibility is that the mechanism leading to the production of anti-AChR antibody is the same in all subjects but the subsequent course of the pathological process and the expression of the disease vary because of genetic factors that influence the individual's immune responsiveness. Although the mean titre of anti-AChR antibody varies between the groups, there is no evidence at present to suggest that genetically linked differences in the pattern of anti-AChR antibodies contribute to the clinical groupings. We therefore favour the alternative explanation that more than one mechanism underlies breakdown in tolerance to AChR and that HLA genotype renders individuals susceptible to one or other of these different mechanisms. The cellular interactions concerned in controlling antibody production are complex and involve subsets of helper and suppressor T lymphocytes. There are likely to be several points at which disordered function could result in breakdown in self-tolerance, and the factors that precipitate the pathological change may themselves be diverse, thus leading to different forms of the disease. This view is consistent with the principal similarity between the different clinical groups, namely, the presence of anti-AChR antibody, and most readily accounts for the varied age of onset, thymic pathology, clinical pattern and response to immunological treatment.

SUMMARY

The clinical manifestations of myasthenia gravis are due to the presence of anti-acetylcholine receptor antibody which is detected in over 90 per cent of patients with generalized weakness. The events which precede the development of abnormal quantities of anti-acetylcholine receptor antibody are unknown and may not be the same in all patients. We have investigated the hypothesis that more than one mechanism may be involved in the breakdown in tolerance to the antibody by comparing clinical characteristics (age at presentation, sex, severity of the disease at the peak of the illness and association with other immune diseases), thymic pathology (thymoma or non-tumourous changes) and immunological observations (titres of limb and ocular anti-acetylcholine receptor antibody, the presence of striated muscle or other auto-antibodies and HLA-A, B, C and DRw typing) in 68 patients with myasthenia gravis.

Many associations were demonstrated between these factors and three groups of patients were identified.

Group A was characterized by thymoma, high titres of anti-acetylcholine receptor antibodies and the presence of striated muscle antibody, but a low frequency of other auto-antibodies and other immune diseases. There were no sex or HLA antigen associations.

Group B was characterized by patients without thymoma presenting at less than 40 years of age in whom titres of anti-acetylcholine receptor antibodies were intermediate. This group had a low frequency of striated muscle antibody, an intermediate frequency of other auto-antibodies, and a very low frequency of other immune diseases. There was an association with females and the presence of HLA-A1, B8 and/or DRw3.

Group C was characterized by patients without thymoma presenting at more than 40 years of age in whom titres of anti-acetylcholine receptor antibodies were low. This group had an intermediate frequency of striated muscle antibody and a high frequency of other auto-antibodies but not of other immune diseases. There was an association with males and the presence of HLA-A3, B7 and/or DRw2.

Our results suggest that the different forms of the disease in these patients arise as a consequence of different mechanisms of breakdown in tolerance. The role of the HLA system in myasthenia gravis appears to be concerned more with determining the susceptibility of the individual to particular mechanisms causing breakdown in tolerance than with determining the characteristics of the resulting immune response.

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Reprint requests to Professor J. Newsom-Davis, Department of Neurological Science, Royal Free Hospital, Pond Street, London NW3 2QG.

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GLIOMATOUS TRANSFORMATION AND DEMYELINATING DISEASES

by MILNE ANDERSON,[1] BRODIE HUGHES, MICHAEL JEFFERSON,
W. THOMAS SMITH *and* J. A. H. WATERHOUSE

(*From the Department of Neurology, The Queen Elizabeth Hospital, Birmingham B15 2TH, the Departments of Neurosurgery, Pathology, and Social Medicine, University of Birmingham, The Medical School, Birmingham B15 2TJ*)

INTRODUCTION

THE development of intracranial gliomas in patients with demyelinating disease, particularly multiple sclerosis (MS) and its variants, is apparently rare, only sixteen instances having been reported before 1977 (Scherer, 1938; Munch-Petersen, 1949; Zimmerman and Netsky, 1950; Matthews, 1962; Brihaye, Perier and Stenuit, 1963; Barnard and Jellinek, 1967; Boyazis, Martin, Bouteille, Guazzi and Manacorda, 1967; Aubert, Arroyo, Daumas and Tripier, 1968; Russell and Rubinstein, 1971; Matthews and Moossy, 1972; Reagan and Freiman, 1973; Currie and Urich, 1974). Whether the concurrence of the two diseases is coincidental or the result of a causal relationship has not been established and opinions differ. Brihaye *et al.* (1963), Matthews and Moossy (1972), and Munch-Petersen (1949) favour chance as the explanation, but Scherer (1938), Russell and Rubinstein (1971), Reagan and Freiman (1973) and Currie and Urich (1974), incline to the other view. We have made a detailed clinical and pathological study of three patients with demyelinating disease, each of whom during the course of his illness developed a glioma from the effects of which they succumbed. Our findings suggest that the tumour developed from neoplastic transformation of glia in areas of established demyelination. Cases 1 and 2 showed distinct evidence of classical MS, and Case 3 resembled atypical neuromyelitis optica and also, to some extent, so-called concentric lacunar leucoencephalopathy (Grcevic, 1960; Currie, Roberts and Urich, 1970).

CASE REPORTS

Case 1

Male, aged 47 years at death. Eight years before death he developed impairment of gait which slowly progressed, to result in spastic paraplegia and urinary incontinence. This was associated with dysarthria and retrobulbar neuritis. A clinical diagnosis of MS was made and he was treated with arsenic in the form of NAB (a regimen then still widely used), which proved ineffectual. During the year before his death he developed left-sided epileptic fits, which affected his face and culminated in an episode of focal status epilepticus which led to his emergency admission to the Queen Elizabeth Hospital, Birmingham.

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[1] *Present address: The Midland Centre for Neurosurgery and Neurology, Holly Lane, Smethwick, Warley, West Midlands B67 7JX.*

On examination he was semicomatose and dysarthric. There were bilateral pallor of the optic discs, weakness of the left side of his face and of his left arm, spastic paraplegia, and bilateral extensor plantar responses. Despite anticonvulsant treatment his left-sided fits continued. A right cerebral hemisphere tumour was suspected and although it was intended that arteriography should be performed his condition deteriorated and he died of bronchopneumonia within ten days of admission.

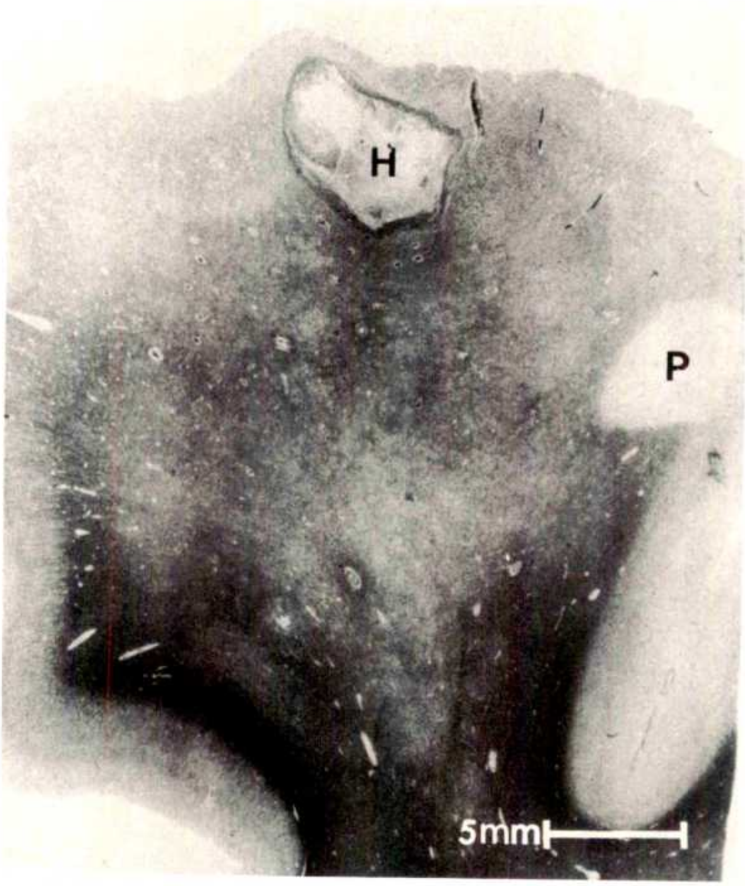

FIG. 1. *Case 1*. Old encapsulated cystic hæmorrhage (1 × 1 cm; H) in substance of glioma just beneath the cortical surface of the right frontal lobe. Around this is a diffuse pale-staining gliomatous tumour, merging with a subcortical plaque (P) of multiple sclerosis. Luxol fast blue/cresyl fast violet.

Pathological findings. Necropsy was carried out eighteen hours after death (EN 245/55). The only abnormality outside the nervous system was bronchopneumonia. The brain did not appear swollen and on the external surface a pigmented area of 'old hæmorrhage' was seen within the cortex of the right precentral gyrus, close to the midline. On sectioning the fixed brain a grey 'translucent' neoplasm was found beneath the pigmented area, 7 cm in cross section, which extended forwards into the right frontal lobe to merge gradually with surrounding normal tissue; within the substance of the tumour was an old encapsulated cystic hæmorrhage, continuous with the pigmented area of overlying cortex (fig. 1). Throughout the brain were many discrete plaques of demyelination, typical of chronic MS and located mainly in sub-cortical white matter and beneath the ependyma of the lateral ventricles (fig. 2). The plaques were clearly defined, measured 0.2–1.5 cm in cross section and were firm, grey-coloured, and slightly depressed below the cut surface of the brain. Similar plaques were scattered throughout the spinal cord.

There was continuity between at least one demyelinated sub-cortical plaque and the tumour in the right frontal region (fig. 1).

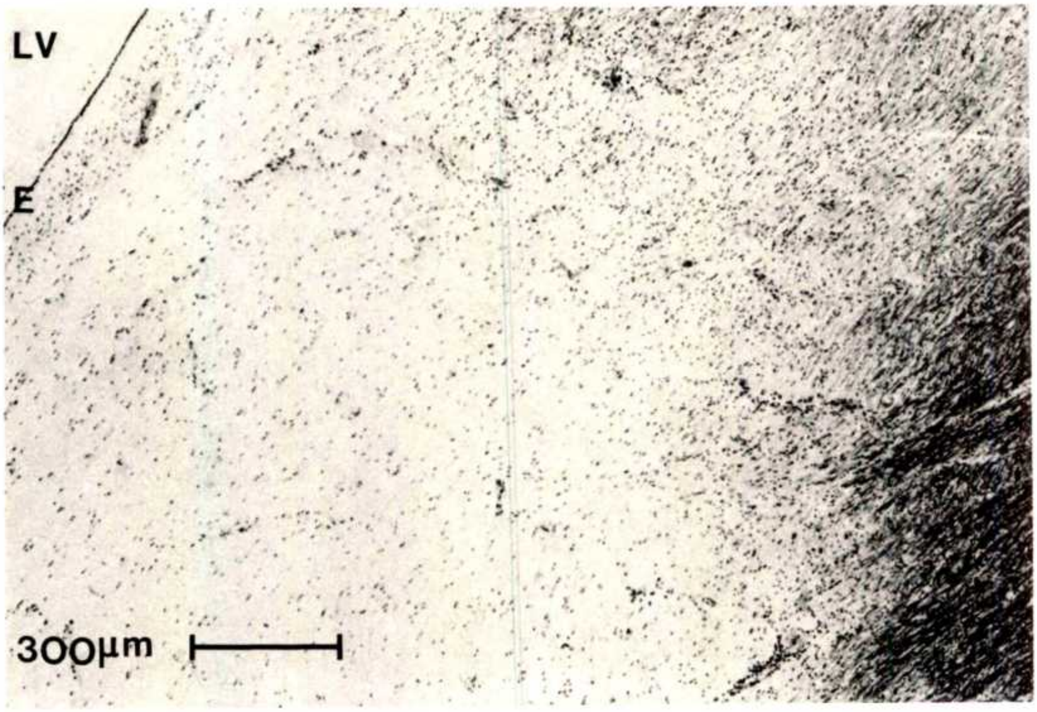

FIG. 2. *Case 1.* Margin of subependymal plaque, including many typical small, dark-staining, round oligodendrocyte nuclei. Towards the centre of the plaque (left half of figure) there are far less nuclei, which are mainly astrocytic in type, and the myelin has disappeared. The ependymal lining (E) of the lateral ventricle (LV) is in the left upper corner. Luxol fast blue/cresyl fast violet.

Histology. The plaques of demyelination showed fibrous gliosis, contained very few sudanophil lipophages, and their margins showed cellular proliferation which included many typical oligodendrocytes (fig. 2). The tumour was a pleomorphic astrocytic glioma showing areas characteristic of pilocytic astrocytoma, of oligodendroastrocytoma and of glioblastoma multiforme (fig. 3); foci of calcification were prominent. Continuity between tumour and plaques of demyelination was evident (fig. 4). Occasional nuclei of tumour cells and of adjacent 'normal' astrocytes and oligodendrocytes contained eosinophilic inclusions. There was no significant infiltration with inflammatory cells.

Case 2

Male, aged 45 years at death. For eleven years he had noticed that after walking for about half a mile he would become unsteady and his legs would feel weak. With rest these symptoms would resolve, but they became increasingly troublesome so that three years before admission he was obliged to consult his family doctor, who found no abnormality on clinical examination. The symptoms persisted, and the unsteadiness became worse. Two years later he was admitted as an emergency to the Queen Elizabeth Hospital, Birmingham, with a history of headache, drowsiness, confusion and ataxia of gait, tending to fall to the left, increasing for the previous three weeks.

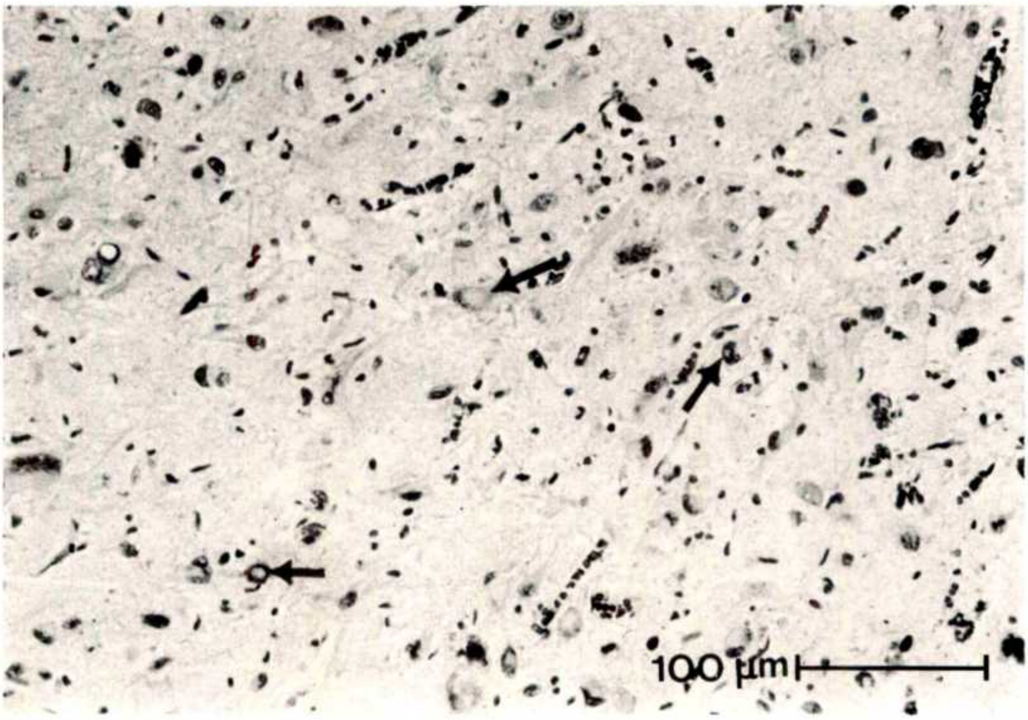

FIG. 3. *Case 1*. Pleomorphic tumour including large, bizarre cells with multiple nuclei and occasional nuclear inclusions (arrow). Hæmatoxylin and eosin.

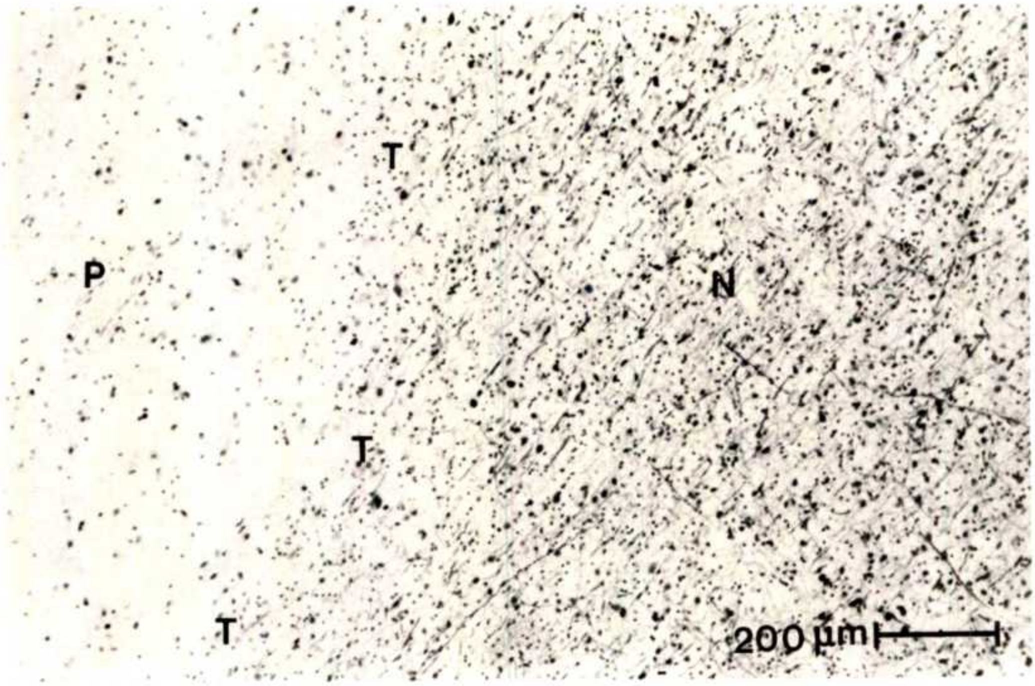

FIG. 4. *Case 1.* Point of transition (T) between 'reactive' astrocytic proliferation in the demyelinated subcortical plaque (P) shown in fig. 1 and neoplastic astrocytic proliferation (N) where the myelin density is reduced. Luxol fast blue/cresyl fast violet.

On examination he was very drowsy, disorientated and dysarthric. There was bilateral papillœdema with hæmorrhages, palsy of conjugate right lateral gaze, and horizontal nystagmus on left lateral gaze. Sensation was disturbed over the left side of his body, on which side the limbs were also hypotonic and ataxic. Deep tendon reflexes were increased on the right, and the right plantar response was extensor.

Air ventriculography demonstrated enlargement of both lateral and third ventricles, and indentation of the frontal horn of the left lateral ventricle; the third ventricle was displaced to the right. It was considered that there was a tumour of the posterior fossa and a subfrontal mass on the left, the former being the more urgent. Exploration of the posterior fossa with biopsy of the left cerebellar hemisphere was undertaken, but no tumour was found. The patient's condition deteriorated and he died one week later.

Pathological findings. Necropsy was carried out fifty-four hours after death (EN 303/65). Apart from bronchopneumonia the abnormalities were confined to the CNS. The brain was œdematous, and there was herniation of the left hippocampal gyrus through the tentorial hiatus. A tumour mass was involving the posterior part of the left frontal lobe, elevating the left anterior cerebral artery and extending behind the optic nerves and chiasma to compress the region of the lamina terminalis and infiltrate the anterior perforated substance (fig. 5). Coronal sections of fixed brain showed the tumour to be centrally situated, 4 × 5 × 6 cm in dimension, with areas of hæmorrhage and necrosis. It extended from 2.5 cm behind the frontal poles to the level of the mamillary bodies and infiltrated the left putamen, anterior thalamus, and white matter of the ventral portion of left frontal lobe to compress the left lateral ventricle to a horizontal slit. Throughout the cerebral hemispheres were numerous small grey clearly-defined areas of demyelination from 1 to 8 mm in diameter. They were most numerous just deep to the cortex or beneath the ventricular ependyma. Adjacent to the left lateral ventricle there was continuity between subependymal demyelination and tumour tissue (fig. 5). At the level of the Vth nerve on the left side of the pons was a depressed area of demyelination 10 × 7.5 mm and a further area 5 × 8 mm was found in the left cerebellar peduncle. Cerebellum and medulla were normal.

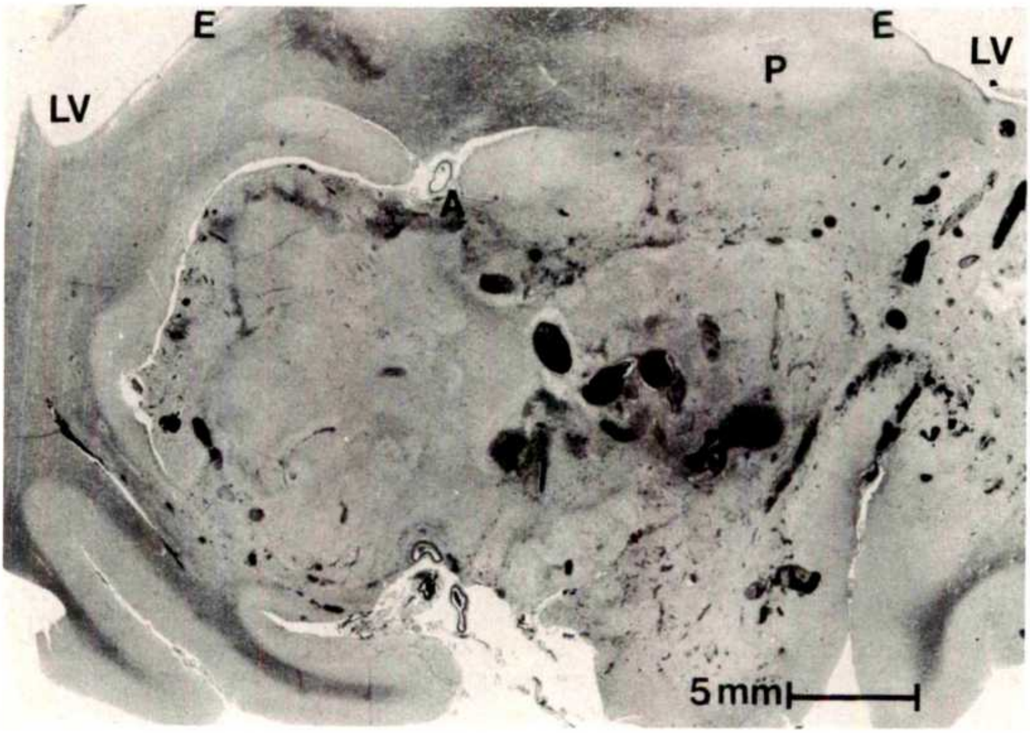

FIG. 5. *Case 2.* Tumour mass infiltrating base of left frontal lobe, elevating left anterior cerebral artery (A), extending across midline to elevate both frontal lobes and compress and elevate both lateral ventricles (LV). A large plaque of demyelination (P) is seen beneath the ependyma (E). Note hæmorrhage and necrosis in tumour. Hæmatoxylin and eosin.

Histology. The areas of demyelination showed only a slight degree of activity, which was demonstrated by peripheral sudanophilic lipophages. In some of the subependymal plaques close to the tumour there were bizarre giant astrocytes

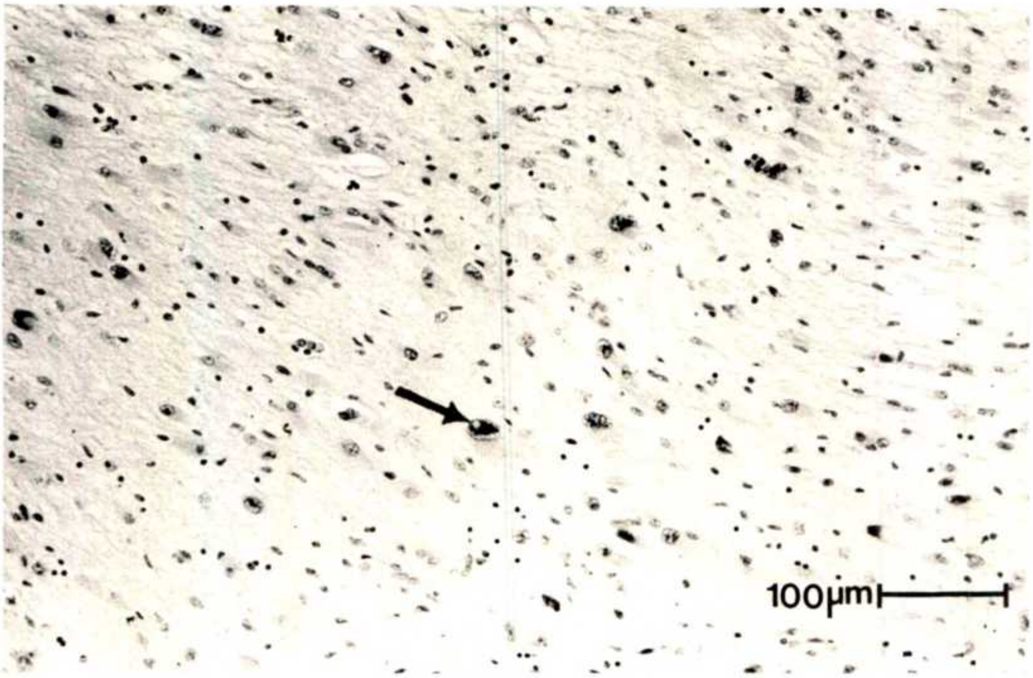

FIG. 6. *Case 2.* Edge of plaque (towards upper margin of fig.) showing astrocytic proliferation in plaque merging below with bizarre pleomorphic glioma cells. A nuclear inclusion is arrowed. Hæmatoxylin and eosin.

(fig. 6), and as plaques merged with tumour there was pronounced proliferation of cells with atypical nuclei, including astrocytes and oligodendrocytes. The tumour was an astrocytic glioma with areas of necrosis and with other areas containing masses of cells with small nuclei and clear cytoplasm suggestive of oligodendro-astrocytoma (fig. 7). Many tumour cells contained acidophilic intranuclear inclusions (fig. 6). In the vicinity of the glioma, and in relation to plaques of demyelination, occasional blood vessels showed mild to prominent cuffing with lymphocytes, phagocytes, and a few plasma cells.

Case 3

Male, aged 45 years at death. At the age of 16 years he lost the vision of both eyes in the course of a few hours. There was only minimal recovery and he was registered as a blind person. No further neurological illness befell him until he was 41 years of age, when he began to have temporal lobe fits, manifested as lapses of awareness preceded by olfactory hallucination. He was admitted to the Midland Centre for Neurosurgery and Neurology (MCNN) under the care of Dr Macdonald Holmes.

On clinical examination the only abnormalities were bilateral pale optic discs, and a right extensor plantar response. Electroencephalography showed an isolated sharp wave discharge from the right temporal lobe. Slight displacement of the pericallosal arteries to the left was the only abnormality on bilateral carotid angiography, and a pneumoencephalogram demonstrated shift of the lateral ventricles from right to left, without further localizing features. Examination of lumbar cerebrospinal fluid was unremarkable. A diagnosis of epilepsy following neuromyelitis optica was made, with the reservation that intrinsic neoplasia had not been excluded. Anticonvulsants were given, and the patient was kept under outpatient review.

Two years later he was admitted to the same hospital on account of personality change, with depression, confusion and headache. He had three grand mal convulsions. Examination again revealed bilateral pale optic discs; there was also left facial weakness, and plantar responses were extensor. EEG showed bilateral slow wave abnormality, most marked in the right temporal area. At arteriography the displacement of the pericallosal artery noted previously was no longer seen, but the position of the middle cerebral artery was judged to be elevated slightly. Surgery was decided against, and the patient was discharged once again to be kept under outpatient review.

His personality now deteriorated further: he became forgetful, irritable, aggressive and truculent, and he began to wander abroad at night. He was admitted to Barnsley Hall Mental Hospital where temporal lobe and grand mal attacks continued, walking became unsteady, and he became bedridden with urinary and fæcal incontinence. He died of bronchopneumonia thirteen months after discharge from the MCNN.

Pathological findings. Permission was obtained for examination of the brain only (OC 43/67). A circumscribed tumour mass, 3 cm in diameter, was found deep to the gyrus rectus, within the white matter of the right posterior frontal lobe, and surrounded by areas of coarse cystic degeneration, coalescing to form concentric

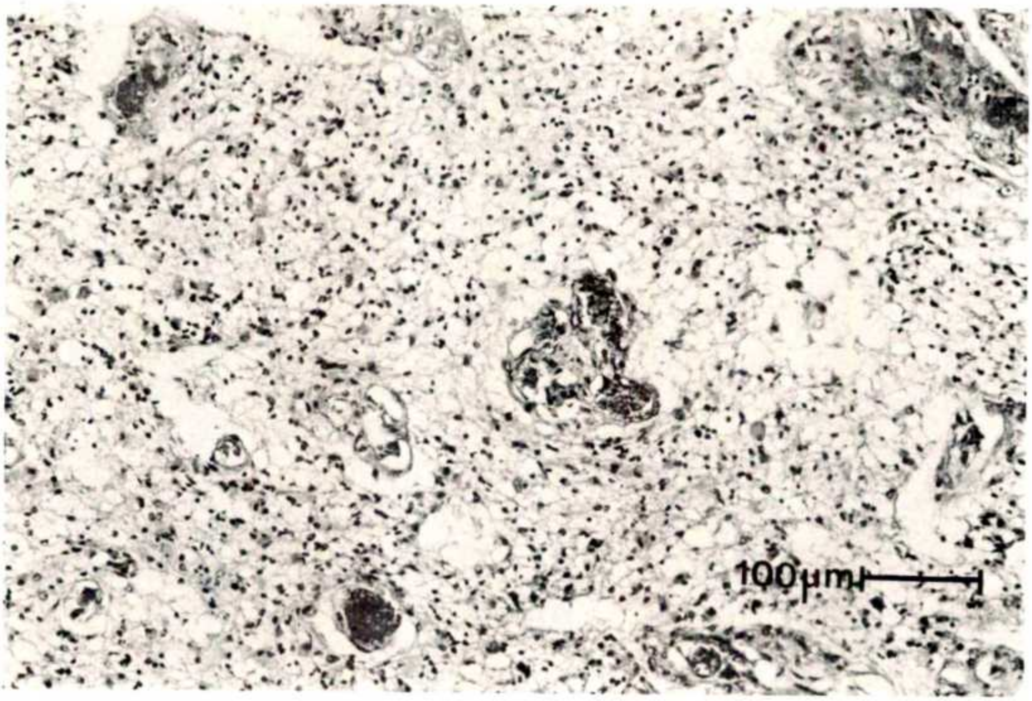

FIG. 7. *Case 2.* Oligodendroastrocytomatous area in tumour, showing thick-walled blood vessels due to endothelial proliferation. Hæmatoxylin and eosin.

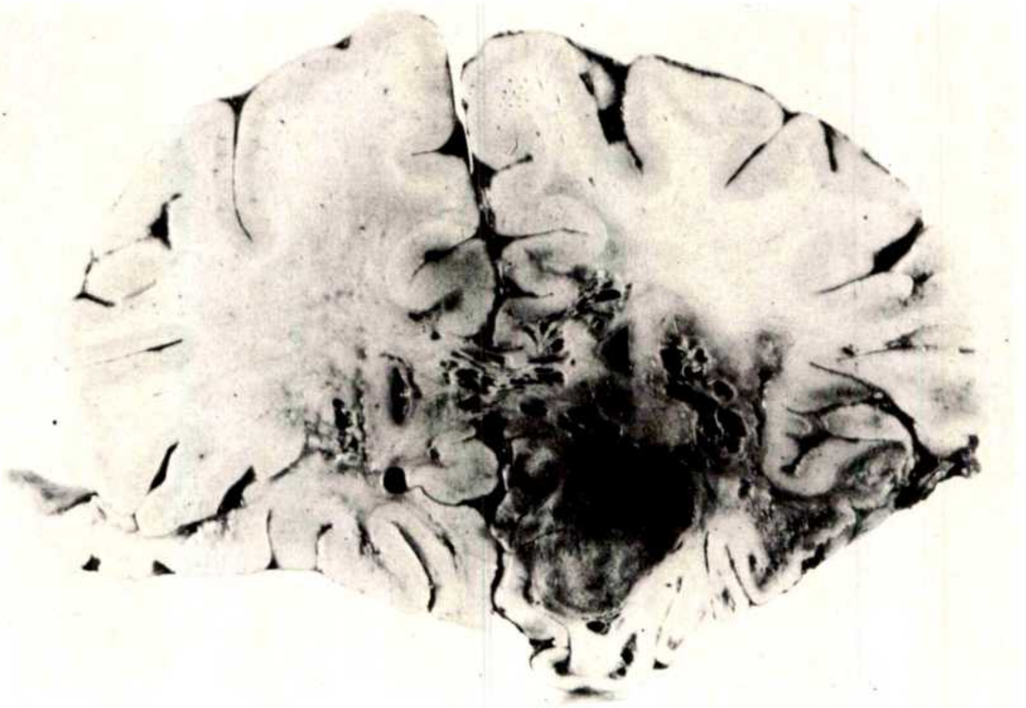

FIG. 8. *Case 3.* Glioma in right posterior frontal region. Note coarse cystic degeneration around tumour, extending across genu of corpus callosum; the cysts have a concentric arrangement. Note grey discolouration (demyelination) in both frontal regions, beyond the cystic foci in the tumour.

lacunæ up to 1 cm in diameter (fig. 8). These areas extended into the white matter deep to the right insula and across the genu of corpus callosum to involve the white matter of the left frontal lobe and insula; there was posterior extension into the right temporal lobe. The anterior parts of both caudate nuclei and putamens were replaced by this process. The subependymal white matter of the frontal and temporal horns of both lateral ventricles showed demyelination and this was continuous with the right frontal tumour around the tips of both frontal horns. The central white matter of the frontal and temporal lobes showed bilateral blotchy grey discolouration and slight softening. Parietal and occipital lobes, brain-stem and cerebellum looked normal.

Histology. Throughout both frontal lobes there was widespread demyelination (fig. 9) extending into temporal white matter to affect the geniculocalcarine fasciculus. There was gross laminar atrophy of both lateral geniculate bodies and patchy atrophy of the calcarine cortex. Axons and myelin sheaths were involved equally in the demyelinating process, which merged gradually with the surrounding 'normal' areas; the subcortical arcuate fibres were spared, as in Schilder-type demyelination (fig. 9). The small number of lipophages containing sudanophilic material suggested that the demyelinating process was quiescent. Microcystic degeneration was widespread, forming the large macroscopically recognizable

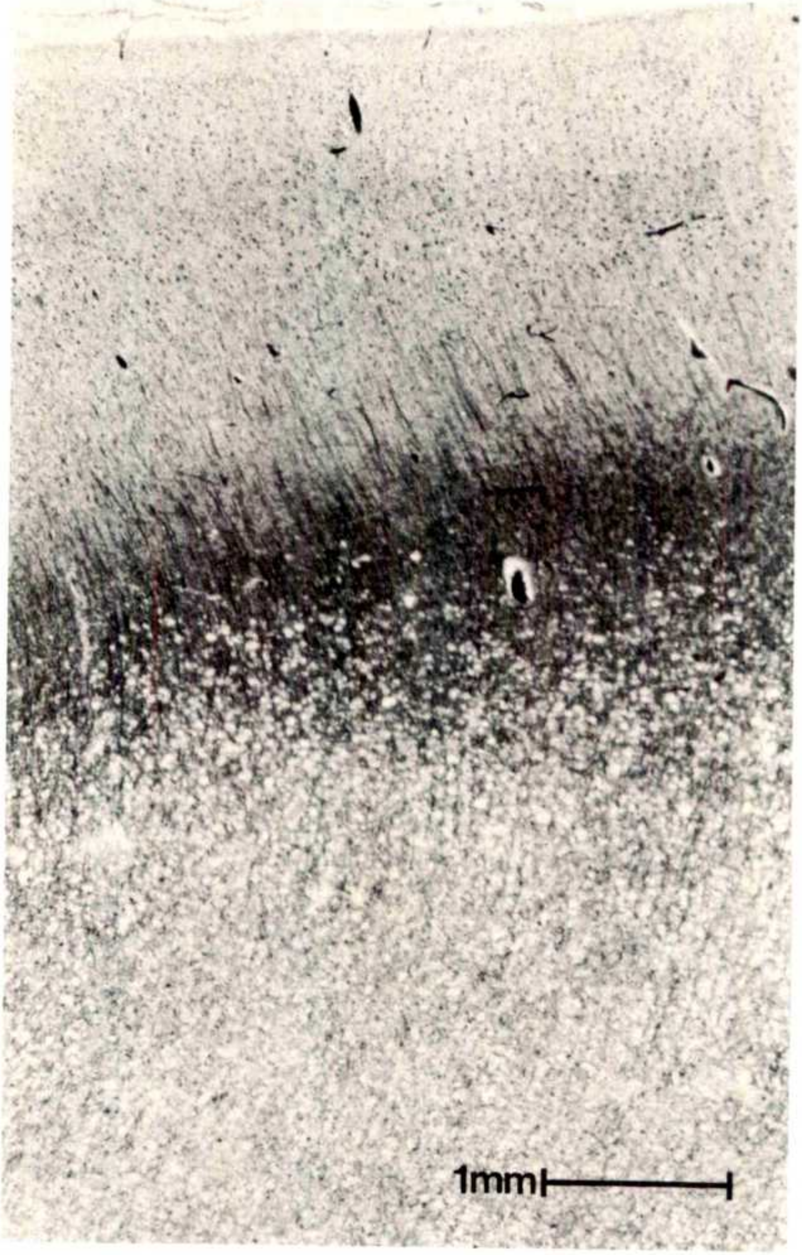

FIG. 9. *Case 3*. Extensive demyelination in subcortical white matter with Schilder-type sparing of subcortical arcuate fibres. Luxol fast blue/cresyl fast violet.

lacunæ by confluence (fig. 10). Small dark oligodendrocyte nuclei were easily identified in the demyelinating areas, which were associated with proliferation of large bizarre bi- or tri-nucleate gemistocytic astrocytes, often with strong eosinophilic hyalinized cytoplasm (fig. 11). Glial fibres staining positively with phosphotungstic acid hæmatoxylin were abundant. The boundary zone between the

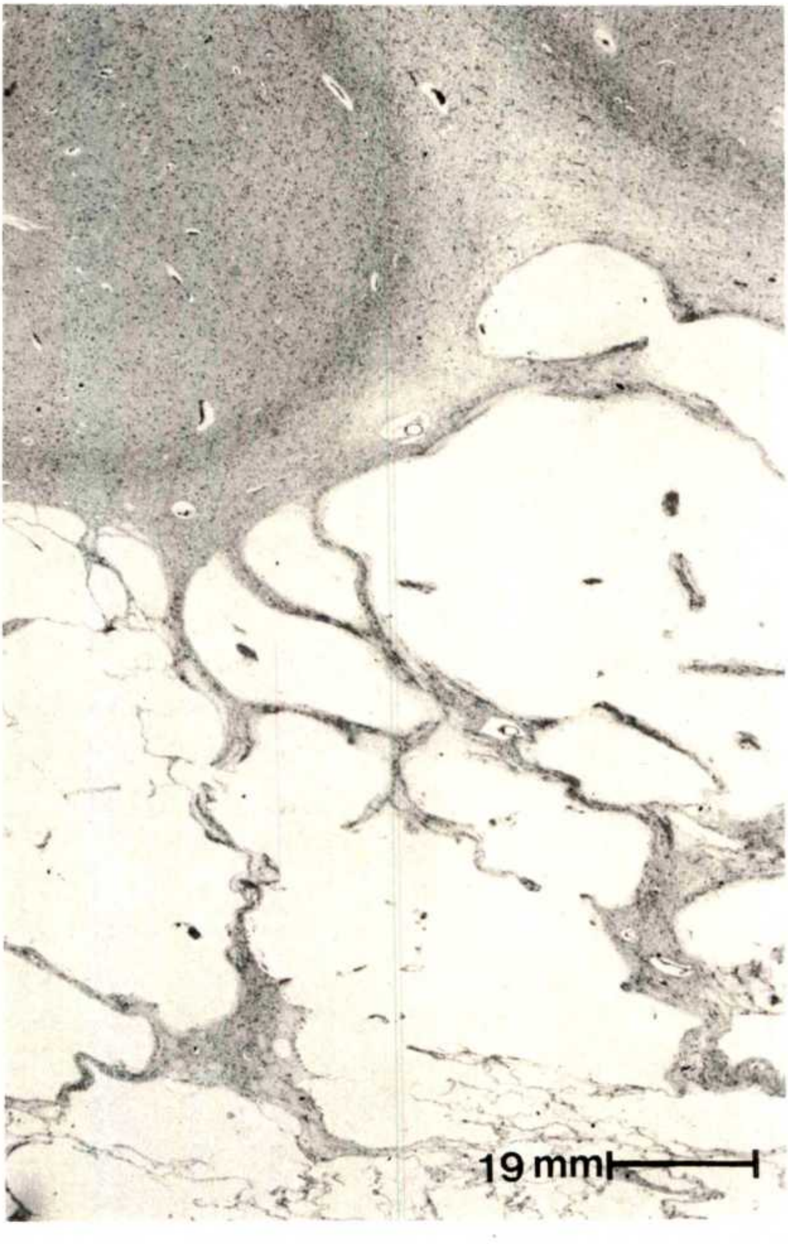

FIG. 10. *Case 3*. Lacunar degeneration in subcortical white matter, forming larger cysts by confluence. Hæmatoxylin and eosin.

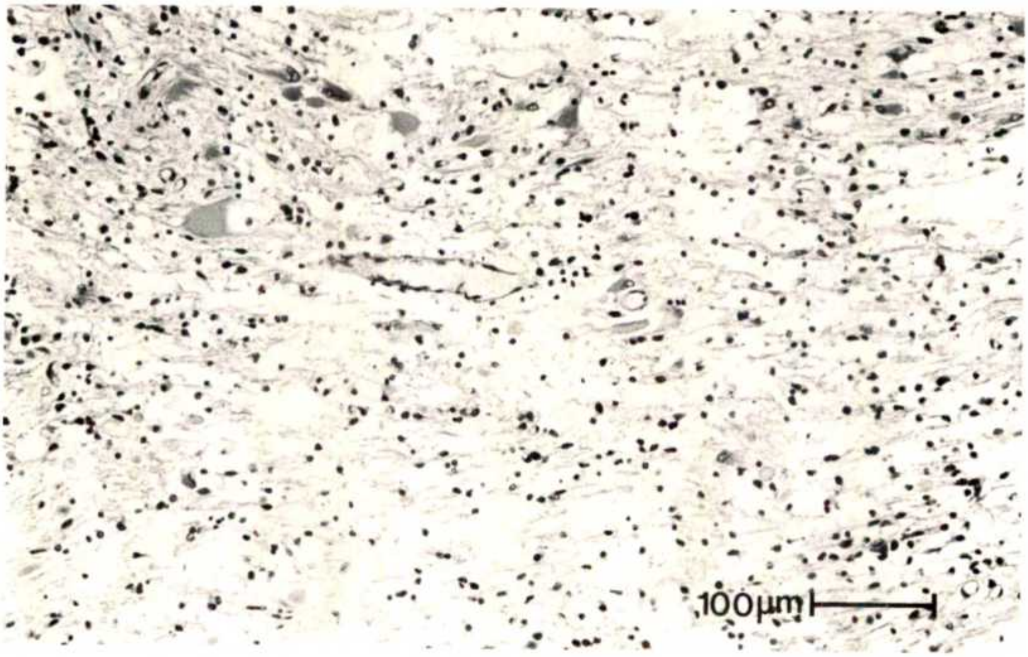

FIG. 11. *Case 3*. Gemistocytic astrocytes, oligodendrocytes, lipophages and myelin fragments in boundary zone between areas of diffuse demyelination and glioma. Thin strands of myelin are still recognizable. Hæmatoxylin and eosin.

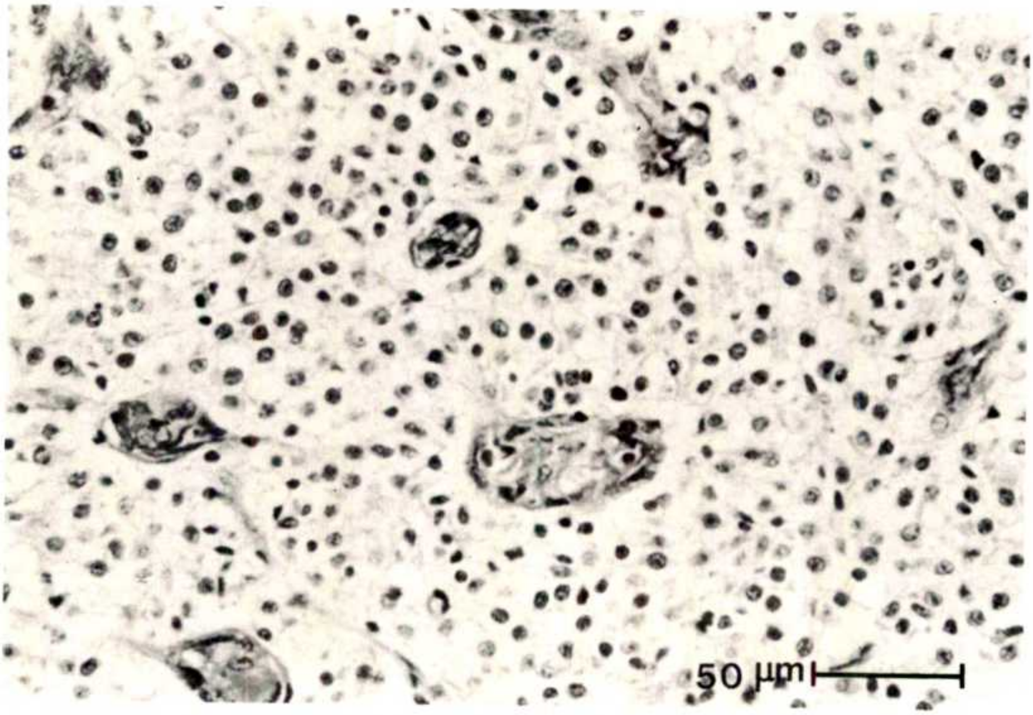

FIG. 12. *Case 3*. Oligodendrocytomatous area. Hæmatoxylin and eosin.

demyelination and neoplasm was poorly defined, and neoplastic infiltration extended into the right temporal lobe and across the genu of the corpus callosum (fig. 8). In many areas it was essentially a well-differentiated oligodendrocytoma (fig. 12), but in places there was considerable anaplasia (glioblastomatous areas) and also admixture with better differentiated astrocytoma (fig. 13). Subpial secondary zones (as described by Scherer (1940)) were seen in the frontal cortex apparently not in continuity with the tumour mass (fig. 14). Intranuclear acidophilic inclusions were present within many of the anaplastic (glioblastomatous) tumour cells (fig. 15).

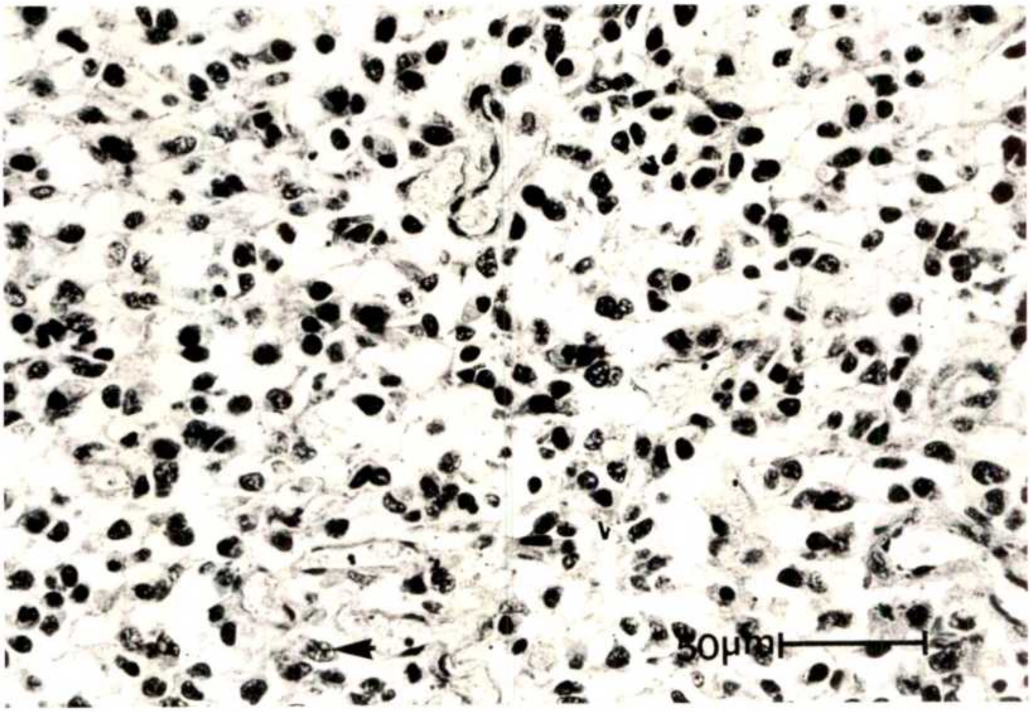

FIG. 13. *Case 3*. Pleomorphic oligodendroastrocytoma including fibrillary, bipolar and multinucleated cells. Hæmatoxylin and eosin.

The areas of lacunar degeneration were subdivided by glial septa of variable thickness (fig. 16), devoid of axons and myelin. Some were extremely slender, but others were much thicker and consisted of proliferating astrocytes, glial fibres, blood vessels and lipophages. In a few places the septa had a vague concentric arrangement (figs. 8 and 10), but this was never very pronounced. There was no significant infiltration with inflammatory cells. The optic chiasma and tracts showed patchy degeneration of myelin and axons (fig. 17), but the optic nerves were not included in the specimen.

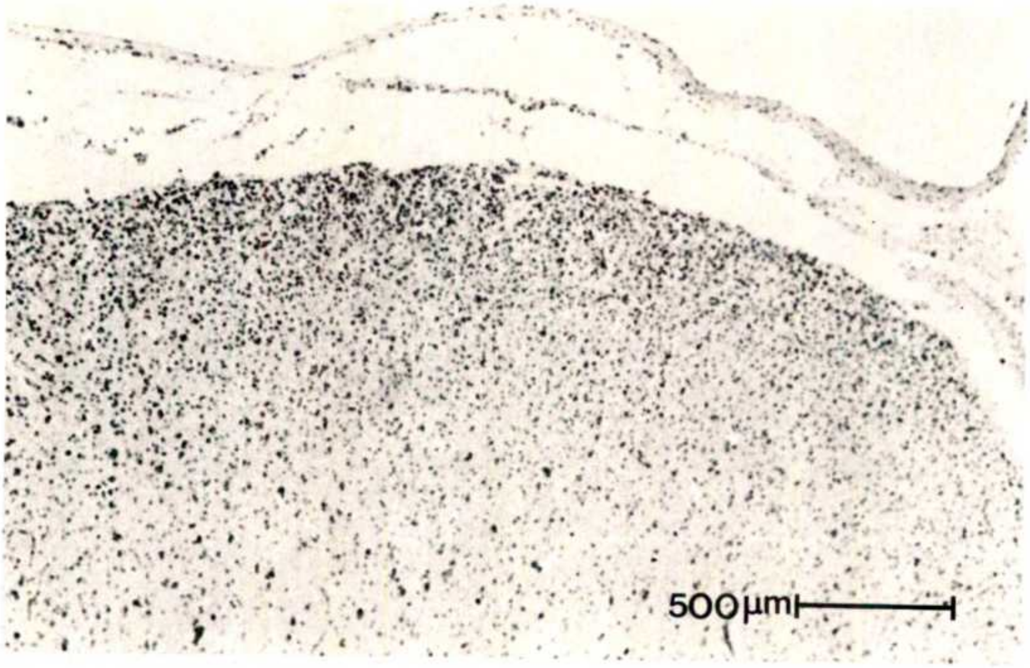

FIG. 14. *Case 3.* Subpial foci of glial proliferation in frontal lobe beyond the confines of the overt tumour (so-called secondary structures of Scherer). Hæmatoxylin and eosin.

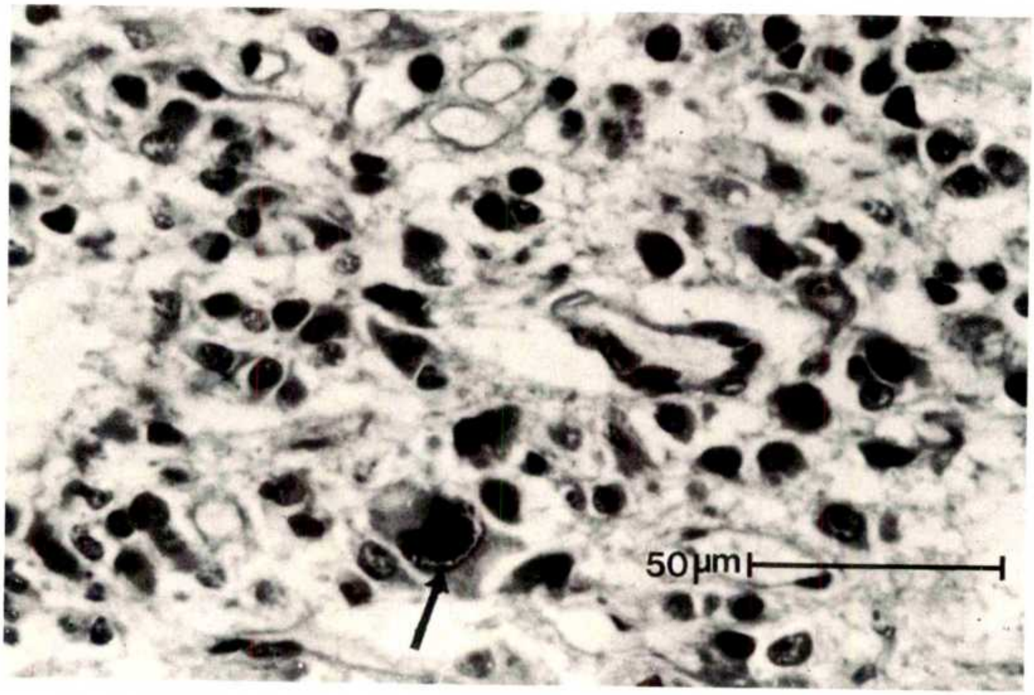

FIG. 15. *Case 3.* Pleomorphic anaplastic tumour cells. Inclusion arrowed. Hæmatoxylin and eosin.

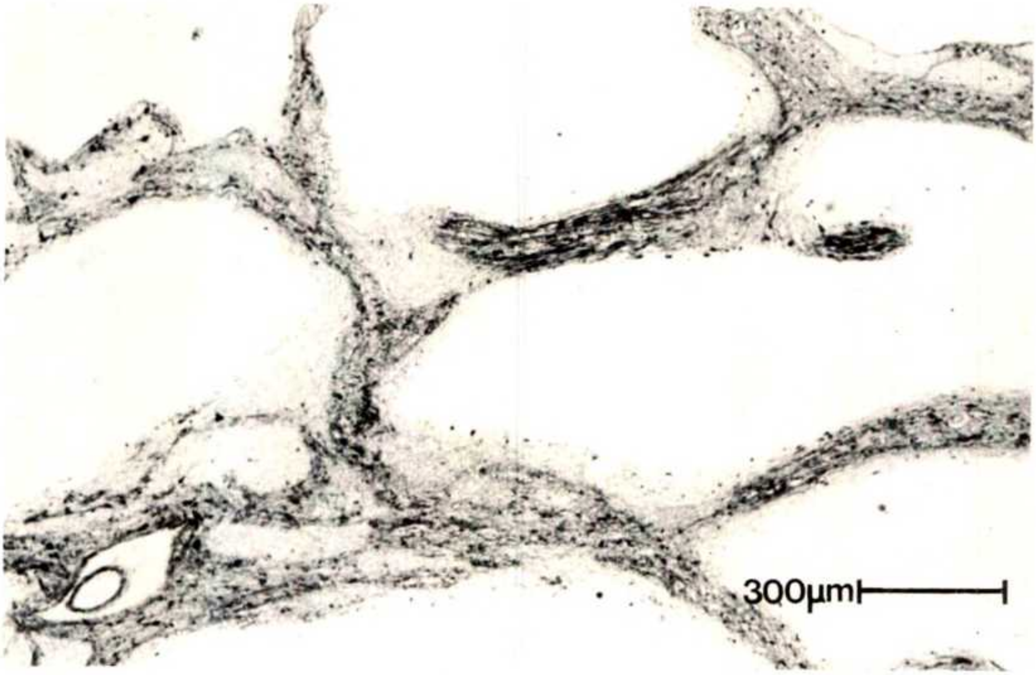

FIG. 16. *Case 3.* Septa of varying thickness between lacunæ in area of demyelination; septa consist of piloid astrocytic cells and fibres, devoid of myelin or axons. Phosphotungstic acid/hæmatoxylin.

DISCUSSION

All three cases demonstrated gradual histological transition from areas of demyelination with gliosis to overt glial tumour. Clinically each patient suffered from the effects of the demyelinating disease for several years before the declaration of symptoms attributable to the tumour. It is our view that this temporal sequence of events and the histological findings suggest a causal relationship between the two, and imply neoplastic transformation of the gliosis associated with the demyelination. A precedent for co-ordinated stromal repair and parenchymatous regeneration undergoing transformation into disordered neoplasia has long been recognized in other tissues outside the nervous system. It is well documented that pulmonary neoplasms may arise in lung tissue previously scarred by tuberculosis, and it is also recognized that the fibrosis and nodular regeneration of hepatic cirrhosis may occasionally be complicated by malignant hepatoma, which may be multicentric. Multicentricity has also been described in gliomas complicating demyelinating diseases (Reagan and Freiman, 1973; Currie and Urich, 1974).

The focal lesions of multiple sclerosis characteristically evolve in an ordered and predictable histological pattern. Initially there is breakdown of the original

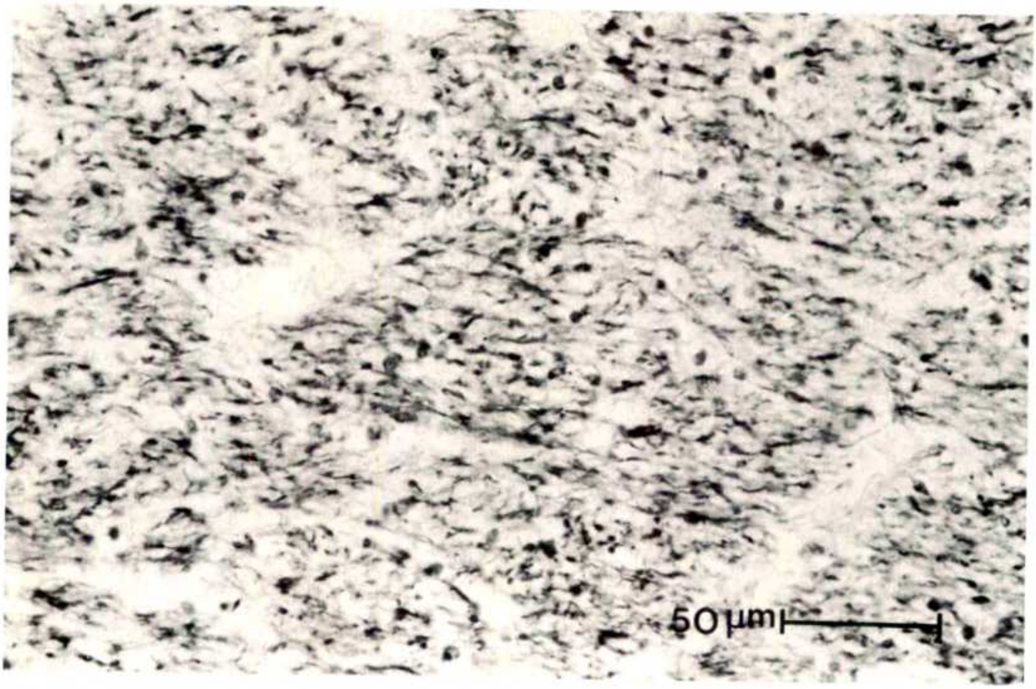

FIG. 17. *Case 3.* Thinning, tortuosity and fragmentation of myelin sheaths in optic chiasma. Luxol fast blue/cresyl fast violet.

lamellar substructure of myelin, which fragments. Simultaneous changes occur in the neuroglia with disintegration and disappearance of oligodendrocytes from the centre of plaques and activation of astrocytes which swell, proliferate and show vigorous formation of glial fibre. Microglia are mobilized in the reactive process, and phagocytose and remove the products of myelin catabolism. With these changes there is marked increase in activity of oxidative and hydrolytic enzymes throughout the plaque. As the plaque ages the initially hypercellular centre shows reduction in cellularity and in enzyme and phagocytic activity; the periphery of the plaque seems to represent a slowly advancing front of active demyelination whilst the centre becomes progressively 'burnt out'.

We consider that development of gliomatous change adjacent to plaques of demyelination is not a chance coincidence and may result from failure of the homeostatic mechanisms which characteristically control macroglial reactions, with consequent transformation to inco-ordinated and infiltrative neoplastic growth. In support of this interpretation contiguity of demyelination and glioma has been demonstrated in each of our 3 cases. Of the 16 cases already reported this relationship was evident in 7. In the case of Scherer (1938) there was diffuse periventricular 'glioblastosis' with transition from areas of acute demyelination.

In that of Brihaye *et al.* (1963) an astrocytoma merged with several patches of demyelination, and in one area similarity was noted between the cells of the tumour and the glia of a demyelinated patch. Case 1 of Russell and Rubinstein (1971) demonstrated a fibrillary astrocytoma had arisen in another small plaque; in their Case 3 a gemistocytic astrocytoma was in continuity with several plaques of demyelination, and a similarity between the astrocytomatous cell types and the reactive neuroglia was noted. The case described by Reagan and Freiman (1973) was of a multicentric anaplastic astrocytoma, and each tumour mass infiltrated plaques of demyelination. In Case 2 of Currie and Urich (1974) there was continuity between a plaque and a malignant astrocytoma; in their Case 3 a glioblastoma overlapped several areas of demyelination. Of the other 9 cases, 7 showed no such association (Munch-Petersen, 1949; Barnard and Jellinek, 1967; Boyazis *et al.*, 1967; Aubert *et al.*, 1968; Matthews and Moossy, 1972; Case 2 of Russell and Rubinstein, 1971; Case 1 of Currie and Urich, 1974). The cases of Zimmermann and Netsky (1950) and of Matthews (1962) are not described in sufficient detail to decide. In our 3 cases there was a definite transition between the cells of the glioma and the reactive astrocytes in the demyelinated areas; it was often impossible to detect the precise point of transition between reactive hypertrophy and hyperplasia and neoplasia. It was also of interest, in view of the fact that myelin is derived from compacted oligodendrocytic cell membrane, that in all three tumours there was an oligodendrocytomatous component. Lumsden (1970) suggested that in MS (and allied demyelinating diseases) it is the oligodendrocyte that is affected primarily, a view held by others before him. He disputed the view of Ibrahim and Adams (1965) that the increase in cellularity and enzyme activity in plaques of MS derive from oligodendrocyte activation and hyperplasia, and he opined that oligodendrocytes disappear from the margin of plaques, where the cellular proliferation and increased enzyme activity may be due to the appearance of microglia.

Inability to demonstrate continuity of the glioma with plaque(s) may be due to the destruction of plaques by the neoplasm in the course of its development. However, an important point raised by Currie and Urich (1974) is that during growth tumours may encroach on other plaques, thus producing the appearance of continuity by collision.

The apparent rarity of concurrence of glioma and demyelination (only 19 known cases, including the 3 of this report) may not be a true reflection of its frequency. Relatively few patients with MS come to necropsy and it is conceivable that in some of these, small gliomas may go unrecognized; the onset of new symptoms and signs due to neoplasm in a patient known to be afflicted with chronic MS could well be dismissed summarily as the result of relapsing demyelination. Similarly, in patients dying with gliomas it is possible that a pathologist will not look for or may miss evidence of demyelination, particularly if there has been no previous clinical suspicion of the disease. At the Queen Elizabeth Hospital in Birmingham in the years 1950–1975 necropsies were carried out on 16 patients who had suffered from MS, 2 of whom (Cases 1 and 2) had associated glial tumours.

From their age at diagnosis of MS and from the duration of their subsequent survival it is possible to calculate the expectation of occurrence of a glioma in either the male or the female series, on the assumption that the incidence rates of the general population should apply. The expected numbers are 0.005 for the males and 0.002 for the females, giving a figure of 0.007 for the combined series, in comparison with two cases observed. The likelihood of such a result occurring by chance alone is extremely small ($P < 0.001$). This reinforces our suspicion that there may be an association between the two conditions.

The presence of a space-occupying mass was suspected from the clinical findings in each of our three cases; this was not proven in Case 1, proven in Case 2, and the evidence was doubtful in Case 3. Since the association of the two conditions has so rarely been reported, the possibility noted above, that deterioration in patients with demyelinating disease may be due to some other cause, particularly the development of intracranial neoplasm, may not be considered and decline may be attributed to a relapse. It is impossible to determine how often this mistake is made. We believe the development of epilepsy in patients already suffering from MS should be viewed with the gravest suspicion and appropriate neuroradiological investigation undertaken. Matthews (1962) codified the opinion of many experienced neurologists when he stated 'that chronic epilepsy is seldom caused by MS, and that fits occurring without obvious relevance to the course of the disease should give rise to suspicion that either the epilepsy is coincidental, or that some other disease has supervened'. Deterioration in conscious level and symptoms which may indicate raised intracranial pressure should likewise not be attributed to demyelination, but should demand search for other cause. In this context Currie and Urich (1974) emphasize the view of Behrman (1966) that glial sclerosis of optic atrophy following demyelination may prevent the development of papillœdema, even though intracranial pressure may be markedly raised.

The demyelination in our Case 3 was unusual in type and in several respects resembled the concentric lacunar encephalopathy described by Grcevic (1960), in which degenerate areas in the brain showed concentric lacunæ separated by glial septa, devoid of axons and myelin sheaths. Currie, Roberts and Urich (1970) described a patient with homonymous hemianopia which rapidly progressed to blindness, to be followed fourteen months later by a fatal ascending myelopathy; lesions in the brain resembled those described by Grcevic (1960) and therefore Currie, Roberts and Urich (1970) suggested that lacunar encephalopathy was closely related to the primary demyelinating deseases, in particular neuromyelitis optica. The cerebral degeneration in our Case 3 also showed some resemblance to concentric lacunar encephalopathy and though, in some respects, the early clinical features pointed to Devic's disease, there was no history of myelopathy. There is no previous record of lacunar degeneration associated with a glioma.

Cases 2 and 3 showed continuity and a gradual transition between gliosis in areas of *subependymal* demyelination and florid gliomatous (predominantly oligodendrocytomatous) neoplasm. This is of interest because of the great cellular activity of glial and neuronal precursors known to occur in the fœtal subependymal region during development of the human and other mammalian brains. Some of this glial activity is probably carried over into adult life. Gliomatous tumours can be induced in many rodents by the administration of carcinomatous N-nitroso compounds (Wechsler, Kleihues, Matsumoto, Zülch, Ivankovic, Preussmann and Druckrey, 1969) and there is a distinct tendency for some of these experimental gliomas to arise in the subependymal region (Jones, Searle and Smith, 1973). It may be that in demyelinating diseases, gliomatous transformation is more likely to occur when the demyelinating process involves this potentially mitotically active subependymal-plate area. In cases in which continuity between subependymal demyelination and glioma is not identified it may still be postulated that transformed precursors of neoplastic cells migrate out from the vulnerable plate-area to give rise to overt glioma elsewhere in the brain.

SUMMARY

The clinical and pathological details are described of three patients with demyelinating diseases associated with a glioma, the effects of which proved fatal. The findings suggest that the tumours developed from neoplastic transformation of glia in areas of established demyelination.

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A NEW METHOD FOR THE MICRODISSECTION OF THE HUMAN HYPOTHALAMUS, WITH MAPPING OF CHOLINERGIC, GABA AND CATECHOLAMINE SYSTEMS IN TWELVE NUCLEI AND AREAS

by HÉLÈNE LANGEVIN *and* LESLIE L. IVERSEN

(*From the MRC Neurochemical Pharmacology Unit, Department of Pharmacology, Medical School, Hills Road, Cambridge CB2 2QD*)

INTRODUCTION

THE distribution and normal degree of variability in the concentration of neurotransmitters and related enzymes in the various nuclei and areas of the human hypothalamus is largely unknown. This information is required before comparative neurochemical studies of the hypothalamus in human diseases can be undertaken. Two complementary techniques have been used for the mapping of neurotransmitters: histochemistry and microdissection followed by neurochemical assays. In the hypothalamus, these techniques have been applied mainly to lower mammals, where the anatomy is more easily defined and tissue preservation is better than in human post-mortem material. In the case of human studies, the microdissection and assay technique offers the advantage of being quantitative and more readily applied to comparisons between normal and diseased groups. There have been only a few studies of the human hypothalamus using this technique. Different approaches to the microdissection have included dividing the hypothalamus into arbitrary cubes (Okon and Koch, 1976), identifying the anatomical structures by alternating stained frozen sections with the sections to be dissected (George, 1978), and photographing the sections before and after the removal of tissues 'punches' to determine their location (Mefford, Oke, Keller, Adams and Jonsson, 1978).

A very important aspect of regional neurochemical studies on human or animal brain is the standardization of a dissection procedure, to permit comparisons between results obtained in different laboratories (Bird, Spokes and Iversen, 1979). In the case of the rat hypothalamus, the development by Palkovits, Brownstein, Saavedra and Axelrod (1974) of a simple and reproducible microdissection technique has led to such a situation. This procedure involves taking samples of fixed volume by punching the frozen tissue at the site of the nucleus with a hollow needle according to standard dissection maps. In the human brain, however, we do not believe this approach to be advisable, as it does not take into account the much greater variation that exists between individual human brains than between those of inbred animals.

This paper describes a novel method for the microdissection of the human hypothalamus which makes allowance for the anatomical differences that exist between cases. The dissection is based on the classical anatomical descriptions of Le Gros Clark (1936), Le Gros Clark, Beattie, Riddoch and Dott (1938) and of Ingram (1940), with some slight modifications according to Nauta and Haymaker (1969). As pointed out by Le Gros Clark, 'although it is difficult to compare the topography of the hypothalamic elements in humans with that of other mammals in coronal sections, due to the deepening of the sella turcica and the forward rotation of the hypophysis . . ., the definition and extent of the nuclear elements are, however, not difficult to see in sagittal sections'. This approach was, therefore, taken as the basis for developing the present dissection method.

In a preliminary study to evaluate the method, the concentrations of dopamine, noradrenaline, adrenaline, glutamic acid decarboxylase, choline acetyltransferase (two enzyme 'markers' for GABA-ergic and cholinergic neurons), GABA, and total protein content were determined in nine randomly selected autopsy cases with no history of neurological disease.

MATERIALS AND METHODS

(1) *Construction of Dissection Maps*

A block containing the hypothalamus was removed from eight randomly chosen human autopsy cases, embedded in paraffin, and serially sectioned with a section thickness of 10 μm, sagittally in five cases and horizontally in three. Every twentieth section was mounted and stained with thionin. In every stained section, the outline of the various tracts, nuclei and areas within the hypothalamus were drawn on tracing paper using a microscope with a drawing tube accessory. Twelve regions were identified and delineated as follows: (the abbreviations listed below will be used in the rest of the text)

VM	Ventromedial nucleus—Le Gros Clark (1936)
DM	Dorsomedial nucleus—Le Gros Clark (1936)
Mam	Mammillary nuclei (medial and lateral combined)—Ingram (1940), Nauta and Haymaker (1969)
Inf	Infundibular nucleus—Nauta and Haymaker (1969)
PV	Paraventricular nucleus—Le Gros Clark (1936), Nauta and Haymaker (1969)
SO	Supraoptic nucleus—Le Gros Clark (1936), Nauta and Haymaker (1969), Defendini and Zimmerman (1978)
Ant	Anterior area—Nauta and Haymaker (1969)
Post	Posterior area—Le Gros Clark (1936), Nauta and Haymaker (1969)
Dors	Dorsal area—Nauta and Haymaker (1969)
Peri	Periventricular area—Ingram (1940), Nauta and Haymaker (1969)
Pre	Preoptic area (including suprachiasmatic area)—Nauta and Haymaker (1969)
Lat	Lateral area (including tuberomammillary and lateral tuberal nuclei)—Le Gros Clark (1936), Ingram (1940), Nauta and Haymaker (1969).

The serial drawings from each case were traced on to perspex sheets and stacked, using the mammillary bodies and the anterior commissure as landmarks, to reconstitute the three-dimensional structure of the whole hypothalamus. The orientated serial drawings were then traced on to a single sheet of paper, to obtain an orthogonal projection of the three dimensional structures in either the sagittal or horizontal plane depending on the plane of section in each case.

(2) *Dissection*

The hypothalamus was removed from nine autopsy cases, with no history of neurological disease or protracted coma before death. The age and sex distribution and causes of death are summarized in Table 1. The mean time interval from death to removal and freezing of the hypothalamic tissue was 46 ± 19 h. In all cases, there was a maximum of 4 h between death and storage of the body at 4° C.

TABLE 1. CLINICO-PATHOLOGICAL DATA ON THE CASES USED FOR DISSECTION

Case No.	*Age (yrs.)*	*Sex*	*Cause of Death*
1	88	F	Liver failure Obstructive jaundice
2	78	F	Acute pulmonary œdema Heart failure
3	49	M	Acute heart failure Rheumatic heart disease
4	58	M	Acute heart failure Old myocardial infarct
5	79	M	Massive pulmonary embolism Carcinoma prostate
6	17	M	Motor vehicle accident Transection aorta
7	66	M	Ruptured myocardial infarct
8	28	M	Motor vehicle accident Cerebral contusion
9	48	F	Motor vehicle accident Multiple injuries

One side of the hypothalamus was used for dissection, which was performed at −9° C, in a modification of the cold box described by Aprison and Hancock (1970). The posterior surface of the hypothalamus was mounted with freezing mounting medium on to the roughened surface of a steel block fastened to a graduated ruler (fig. 1), orientated with the ventral surface of the hypothalamus facing up, and so that the coronal plane of section would be as parallel as possible to the plane of the lamina terminalis. The hypothalamus was cut anteroposteriorly into 500 μm slices with a razor blade against a steel block sliding tightly under the ruler, which had been fastened to the floor of the dissecting box with screws (fig. 1). The thickness of the slices was checked before and after cutting by monitoring the distance moved by the steel block against the fixed ruler with

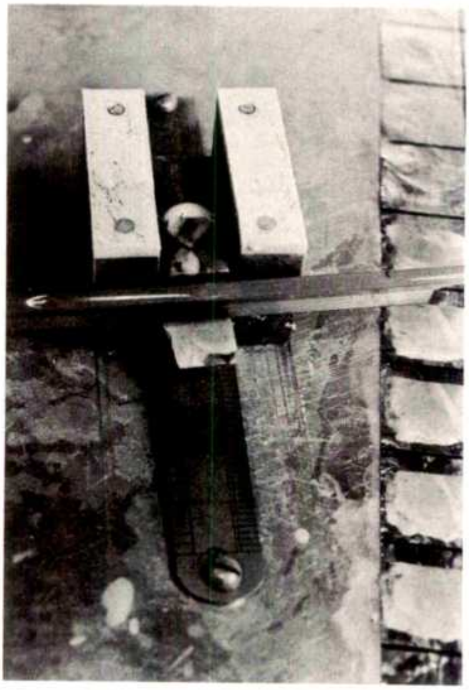

FIG. 1. Sectioning apparatus. The frozen hypothalamus is mounted on to a graduated ruler and sectioned with a razor blade against a steel block sliding tightly under the ruler.

a dissecting microscope. The frozen slices were laid down inside the cold box and numbered. In each slice, the nuclei were removed according to the following outline (*see* fig. 4):

(a) preoptic area: between the first and last slice in which the anterior commissure reaches the midline, width arbitrarily defined as 12 mm at the level of the optic chiasm, tapering up to the fornix;

(b) periventricular area: a thin strip that detaches easily along the edge of the third ventricle, throughout the length of the hypothalamus;

(c) anterior area: as in fig. 4. Lateral extent arbitrarily defined to 4.5 mm from the edge of the third ventricle;

(d) paraventricular nucleus: as in fig. 4;

(e) dorsomedial nucleus: as in fig. 4;

(f) ventromedial nucleus: as in fig. 4;

(g) infundibular nucleus: as in fig. 4. Width arbitrarily defined as 2 to 2.5 mm.

(h) supraoptic nucleus: two parts:

  (i) dorsolateral to optic tract. Approximately 1 mm in vertical and transverse diameters. From AP No. 10 to AP No. 40;

  (ii) medial to optic tract. Slightly smaller than dorsolateral part. From immediately behind the optic chiasm (approximately AP No. 5), to AP No. 30;

(i) posterior area: as in fig. 4 to AP No. 100, then superior to mammillary nucleus and medial to mammillo-thalamic tract. Vertical extent: 7 mm in slice 90—then 7 mm minus the height of the mammillary nucleus;

(j) dorsal area: as in fig. 4;

(k) mammillary nucleus: no distinction made between the medial and lateral mammillary nuclei;

(l) lateral area: from AP No. 0 to AP No. 100: lateral to all structures described above, then, lateral to the mammillo-thalamic tract. Lateral extent at the level of the optic tract arbitrarily defined to 10 mm from the edge of the third ventricle at AP No. 10, 8 mm at AP No. 30, and 7 mm at AP No. 40, and from then on to the visible internal capsule.

The dissected samples were stored at −70° C, and at a later date were weighed, thawed, and homogenized in 1:4 vol (w/v) of water. Five aliquots were immediately taken:

1. 25 μl of the 20 per cent homogenate were further diluted in perchloric acid (PCA) to obtain a 5 per cent homogenate in 0.1 N PCA containing 10 mg per cent EDTA, which was assayed radioenzymatically for dopamine, noradrenaline and adrenaline according to the method described by Emson and Koob (1978);
2. 20 μl were used for the radiochemical assay of choline acetyltransferase (CAT) according to a modification of the method of Fonnum (1969) with ^{3}H-acetyl-CoA as a substrate for the reaction;
3. 10 μl were used for the radiochemical assay of glutamic acid decarboxylase (GAD) according to Roberts and Simonsen (1963);
4. 50 μl were used for the fluorimetric assay of GABA according to Kravitz and Potter (1965);
5. 5 μl were used to determine the total protein content of the sample according to the method of Lowry, Rosebrough, Farr and Randall (1951).

RESULTS

(1) *Dissection Maps and Methods*

Each of eight serial sectioned paraffin-embedded specimens gave rise to a projection on to the plane of section of the various structures of the hypothalamus (on the sagittal plane in five cases and the horizontal plane in three).

For the purpose of this analysis, the hypothalamus is considered as part of a three-dimensional orthogonal space, the origin of which would be the intersection of the coronal plane parallel to the plane of the lamina terminalis and tangent to the posterior edge of the anterior commissure, the sagittal plane going through the middle of the third ventricle, and the horizontal plane tangent to the superior edge of the mammillary body. In this space, the fibres of the fornix within the hypothalamus form a curve, from immediately above and behind the anterior commissure, going caudally, ventrally, and laterally to reach the lateral edge of the mammillary body (fig. 2, *insert*).

Two different representations of this curve are seen in figs. 2A and 2B. In each figure, the average and standard deviation of the projection of the course of the fornix in the sagittal (2A) and horizontal plane (2B) was obtained from tracings of the middle of the bundle of the fornix in the stacked serial drawings of each of five and three cases, respectively. In each case, the distances from the origin to the lateral edge of the mammillary body on the x axis (medial to lateral), to the dorsal border of the anterior commissure on the y axis (ventral to dorsal), and to the anterior edge of the mammillary body on the z axis (anteroposterior), were standardized and divided into 100 units, defining a system of fractional co-ordinates that will be used in the construction of the dissection maps as well as during the dissection.

Fig. 2 enables us to determine the average *x* and *y* co-ordinates of the fornix for any given value of *z*, thereby giving the average position of the fornix in the coronal plane at any level along the anteroposterior axis. The fornix bears relations to most nuclei and areas of the hypothalamus. It is clearly visible on the gross frozen specimens, specially in coronal sections, which are perpendicular to its main axis. It is possible, therefore, during the microdissection of serial coronal slices of the hypothalamus, to use the fornix as a built-in scale, if the average positions of the various nuclei and areas relative to the fornix are known in each slice.

In fig. 3, the sagittal projection of the paraventricular, dorsomedial, ventromedial, and mammillary nuclei, averaged from the five sagittally cut specimens, was added to fig. 2a. The normalized distance between the end of the anterior commissure and the beginning of the mammillary body can be conveniently divided into twenty equal segments, each of five units defining twenty anteroposterior levels (AP levels).

A set of maps of twenty serial coronal slices taken at each of these AP levels was reconstructed from the sagittal and horizontal data. Eleven of these maps are presented in fig. 4. In each map, the *x*, *y* and *z* co-ordinates of the fornix were calculated from fig. 2. The average extent of the ventromedial, dorsomedial and paraventricular nuclei in relation to the fornix in the anteroposterior and dorsoventral direction was determined from fig. 3. The average mediolateral extent of these nuclei was deduced from the mediolateral position of the fornix: the fornix starts off adjacent to the border of the third ventricle; as it courses ventrally, the paraventricular, then the dorsomedial, then part of the ventromedial nucleus are sequentially located between it and the third ventricle.

The three nuclei defined above can serve as a 'core', that bears relations to several other structures, the average position of which can now be defined, such as the anterior, dorsal and posterior areas, and the infundibular nucleus. Other

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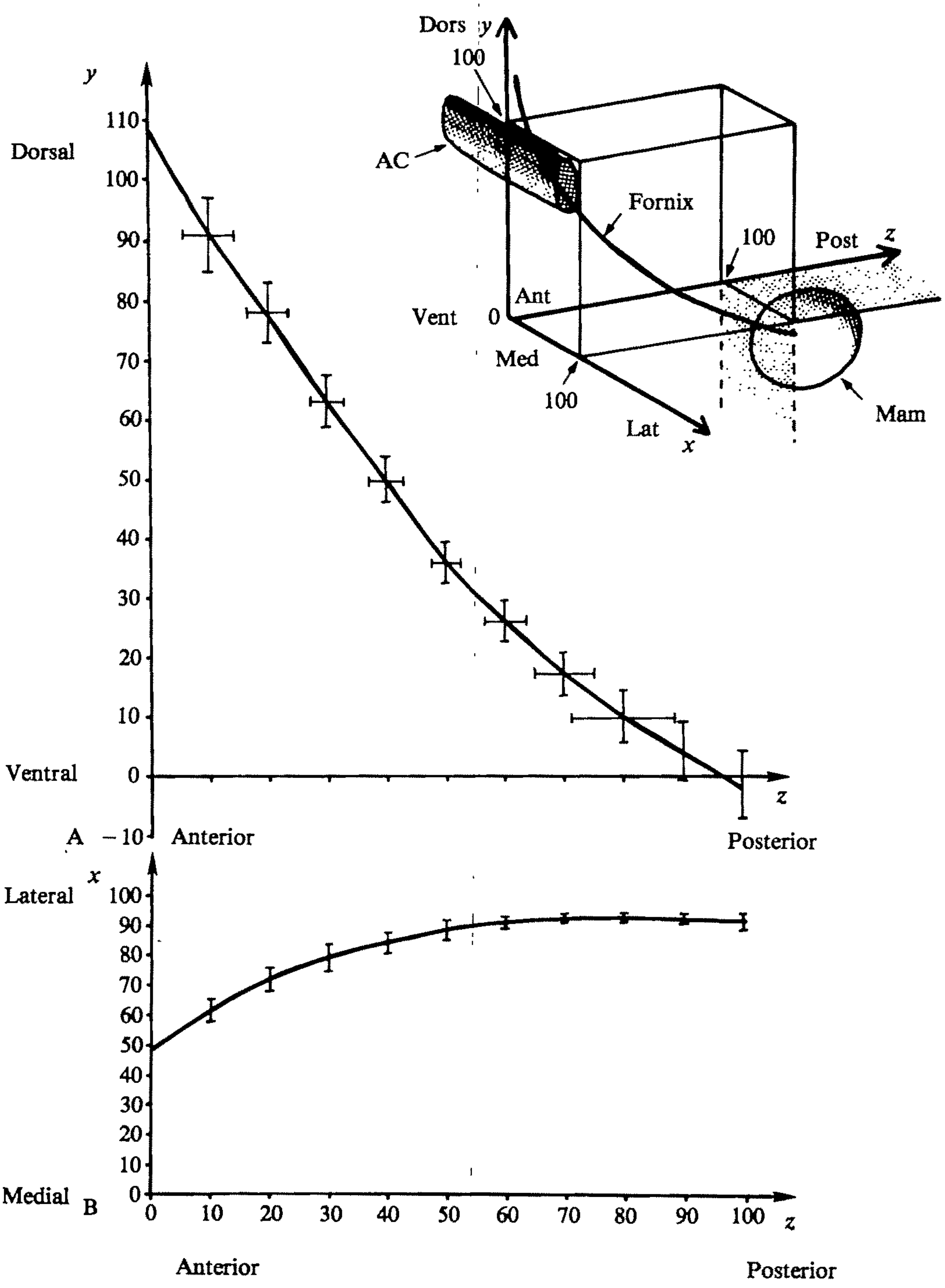
FIG. 2. Representation of the course of the fornix within the hypothalamus. A, sagittal projection; average and standard deviation from 5 cases. B, horizontal projection: average and standard deviation from 3 cases (one bilateral). *Insert*, drawing representing the curve of the fornix in three dimensions, the anterior commissure (AC), and the mammillary body (Mam) in one side of the hypothalamus.

In fig. 2 and in all subsequent drawings: *x* axis = medial to lateral, *y* axis = ventral to dorsal, *z* axis = anterior to posterior. Coronal plane defined by *x* and *y* axes, sagittal plane, *y* and *z* axes, horizontal plane, *x* and *z* axes. The *z* axes in figs. 2A and B are identical.

The following distances were normalized to 100 per cent: on the *x* axis, from midline to lateral edge of mammillary body; on the *y* axis, from dorsal edge of mammillary body to dorsal edge of anterior commissure; on the *z* axis, from posterior edge of anterior commissure to anterior edge of mammillary body, and the total distance divided into equal segments of 10 units.

Different scales were used for the *x* and *y* axes in figs. 2A and B to preserve the realistic appearance of the two curves but fractional co-ordinates are used in both cases.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areas such as preoptic, periventricular and lateral will be defined in a more arbitrary fashion (*see* Materials and Methods section for a complete outline of dissection of the 12 nuclei and areas).

Dissection of the frozen specimens. The hypothalamus is cut coronally through its entire length into 500 μm slices, numbered anteroposteriorly in the following way: the first slice posterior to the anterior commissure in the midline is termed AP No. 0. The first slice containing the mammillary body is termed AP No. 100. The

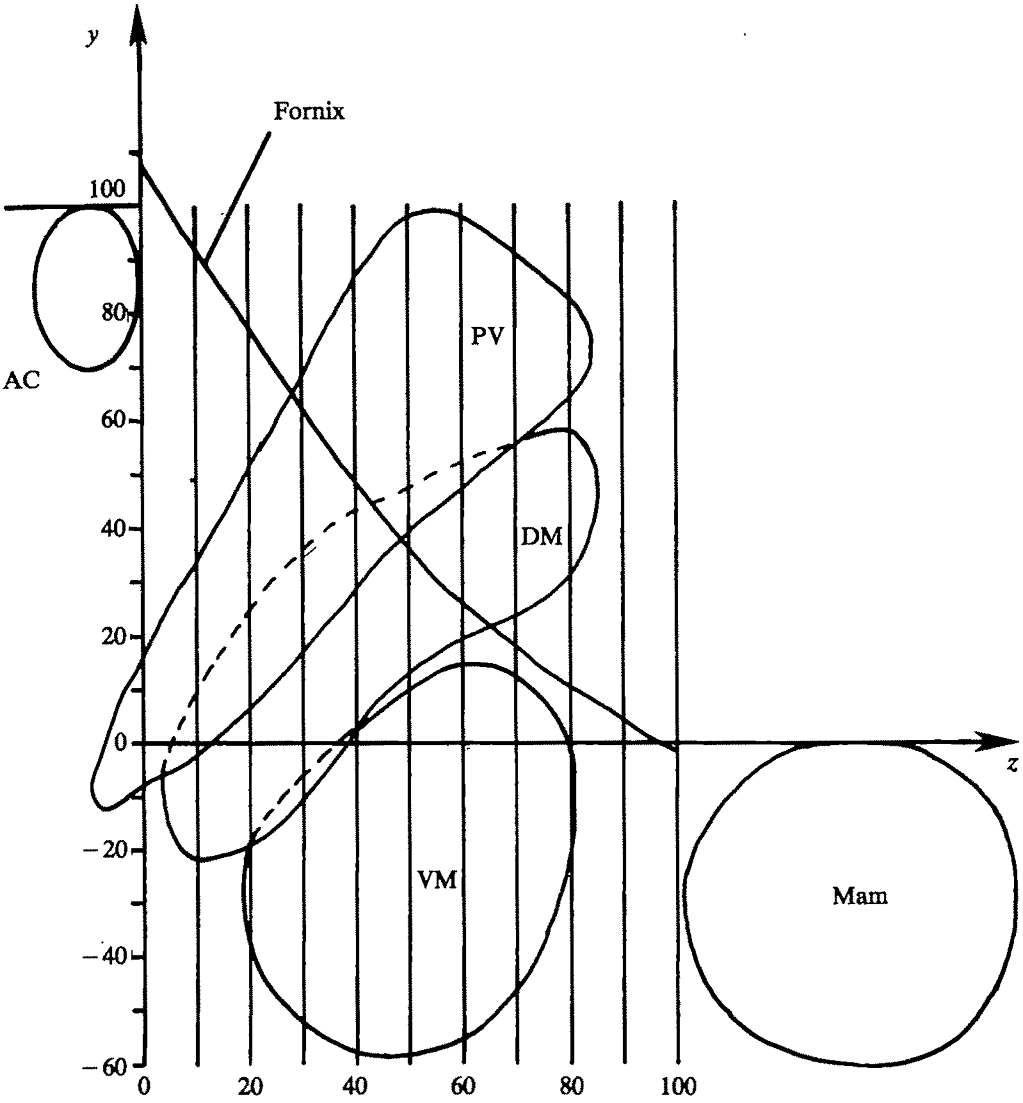

FIG. 3. Sagittal projection of the fornix, paraventricular (PV), ventromedial (VM), dorsomedial (DM) and mammillary (Mam) nuclei, averaged from 5 cases. AC = anterior commissure; x and y axes as in fig. 2. Dotted lines indicate overlap of nuclei, viewed from medial side.

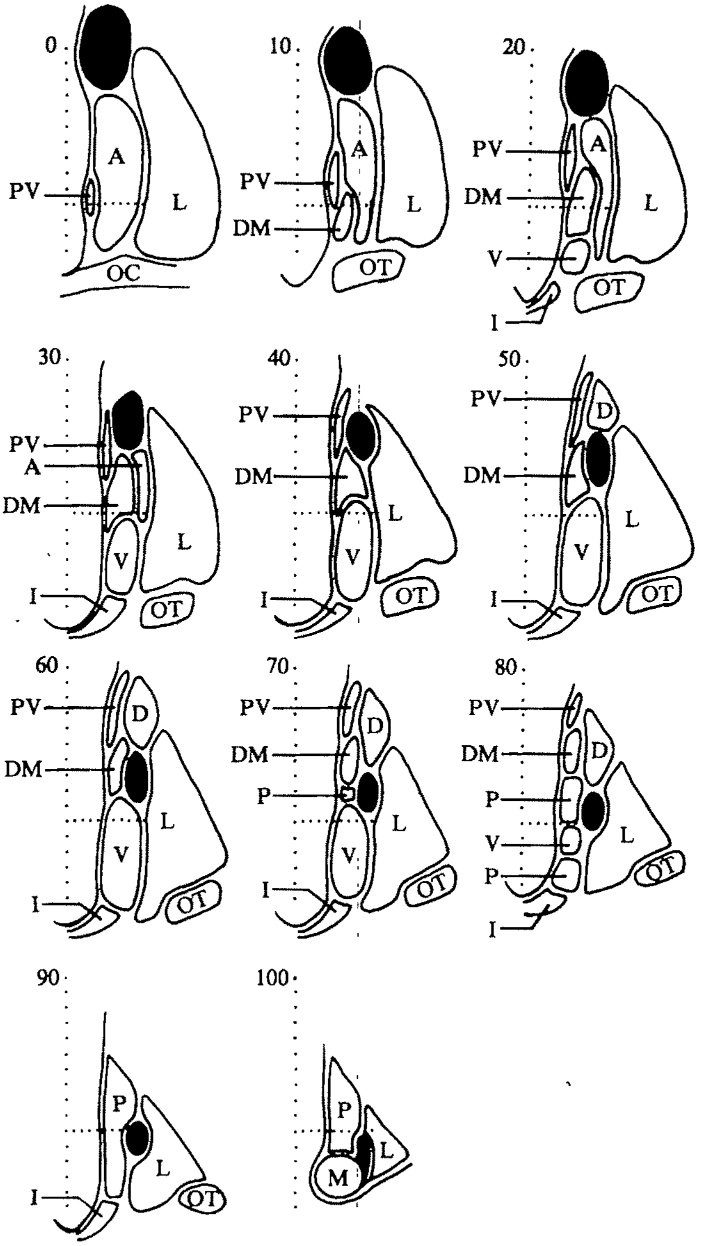

FIG. 4. Diagram of 11 serial coronal sections through the human hypothalamus. The sections are numbered 0 through 100 according to their fractional co-ordinate in the anteroposterior direction (AP level—*see text*). A complete series of 20 maps can be obtained by interpolating between every pair of consecutive maps. In each section the fornix is shown in black and the various nuclei and areas labelled as follows: A = anterior; PV = paraventricular; L = lateral; DM = dorsomedial; V = ventromedial; I = infundibular; D = dorsal; P = posterior; M = mammillary; OC = optic chiasm; OT = optic tract. The dotted scale represents the fractional divisions on the x and y axes in figs. 2 and 3, the x axis being horizontal and the y axis vertical.

slices between 0 and 100 are ascribed AP numbers expressed as a percentage of the total number of slices between slice 0 and 100. Each AP number is approximated to the closest of twenty diagrams, eleven of which are shown in fig. 4. The average position of the nuclei and the fornix are, therefore, applied to individual cases by expressing all measurements as percentages of a variable total distance.

(2) *Distribution of Dopamine, Noradrenaline, Adrenaline, GABA, GAD and CAT*

The mean concentrations and standard deviations for these were determined in the twelve dissected regions (fig. 5 and Table 2). In some areas (periventricular, supraoptic and paraventricular nuclei), the small size of the sample (often under 15 mg wet weight) did not allow enough tissue for all the assays to be performed.

DISCUSSION

One of the major difficulties in the development of a method for the microdissection of human specimens is to achieve a repeatable dissection on tissue that has such high case-to-case anatomical variation by comparison with animal material. The main goal in developing this dissection method was to find a parameter that would not be so variable from case to case, and which could be used as a basis for dissection. It was first apparent that using one or several fixed reference points during the dissection would not be suitable, as they are themselves subject to variation, and an error in the location of these reference points would have a profound effect on all the measurements. A series of connected reference points such as a line or curve visible throughout the hypothalamus is preferable, as it offers direct support all the way through the dissection. When absolute measurements were made on the length and height of the fornix within the hypothalamus, an average standard deviation between cases of 8 to 15 per cent was observed. When only the shape of the curve was considered (by standardizing these distances) it was found to be very constant (*see* fig. 2), and, therefore, a reliable guide to locate structures in serial sections. One reference plane, however, remained crucial to the dissection and was sometimes difficult to see on the frozen specimens, that is the plane of the lamina terminalis used to orientate the block prior to sectioning. The difficulties in using this plane for orientation have been discussed by Christ (1969). Care must, therefore, be taken in defining this plane in a consistent fashion.

The best correlations between the dissected regions and the known anatomical structures would ideally be obtained by staining of frozen sections during the dissection. This approach, used by George (1978), has the disadvantage of being time-consuming and of not permitting the dissection of the whole hypothalamus, as a substantial proportion of the tissue is used up for staining and cannot be assayed. In addition, the coronal plane, most suitable for the dissection, is not, as mentioned earlier, the plane where the stained nuclei are most readily seen. The method presented here does not offer direct anatomical localization, but aims at the repeatable dissection of a given set of carefully defined regions, that could

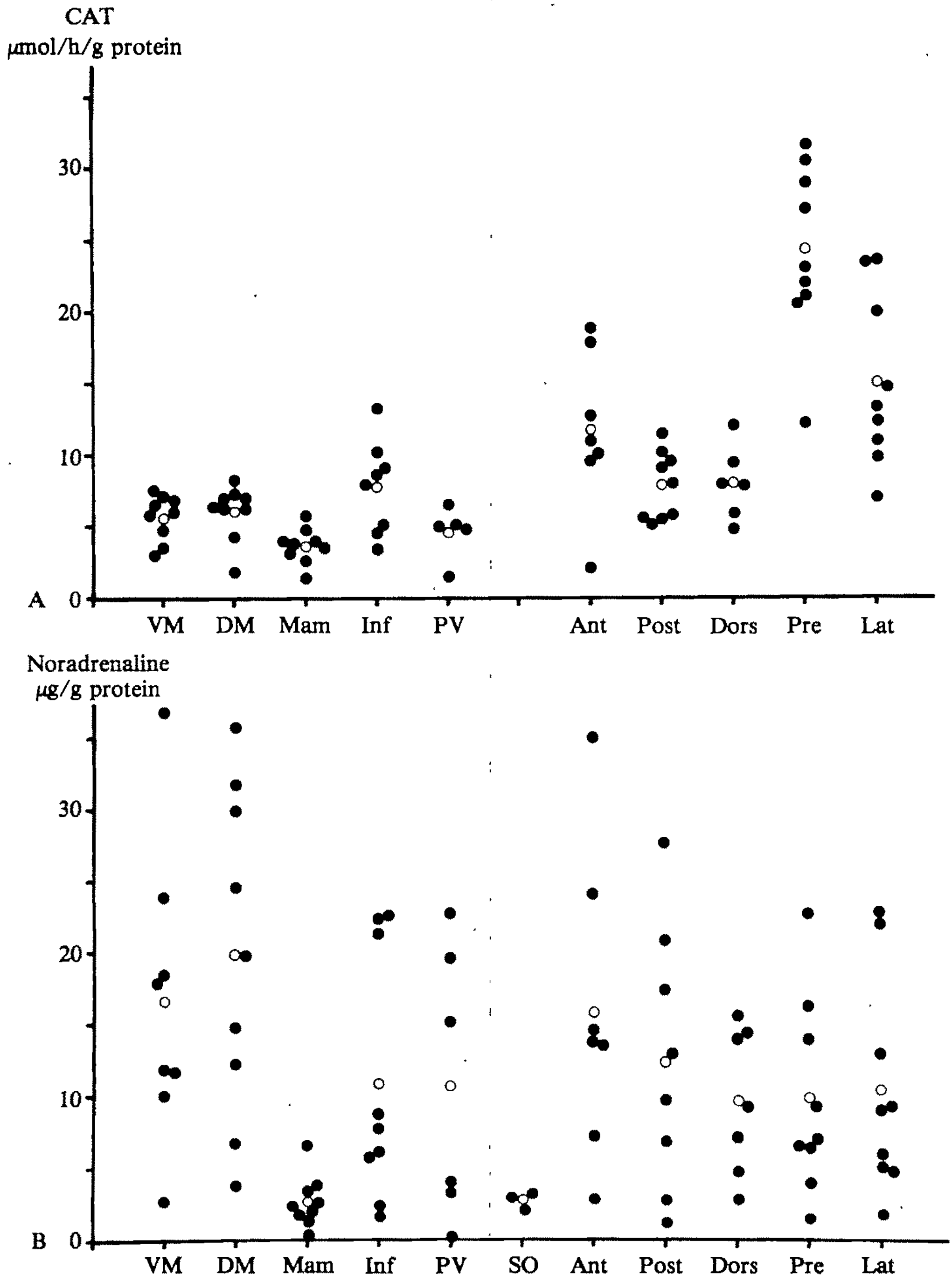

FIG. 5. Diagram illustrating the variable degree of scatter between cases in the concentration of A, choline acetyltransferase compared to B, noradrenaline in subregions of the human hypothalamus. Open circles indicate mean values.

TABLE 2. WET WEIGHT, TOTAL PROTEIN CONTENT AND CONCENTRATION OF CHOLINE ACETYLTRANSFERASE GABA, GLUTAMATE DECARBOXYLASE, DOPAMINE, NORADRENALINE AND ADRENALINE IN 12 REGIONS OF THE HUMAN HYPOTHALAMUS

	VM	*DM*	*Mam*	*Inf*	*PV*	*SO*	*Ant*	*Post*	*Dors*	*Peri*	*Pre*	*Lat*
Wet weight	69.3	42.0	75.9	46.8	22.1	16.0	55.7	74.2	28.1	18.9	157.0	195.0
(mg)	±13.1	±10.9	±10.9	±18.3	±8.9	±5.0	±28.6	±13.5	±9.2	±18.6	±73.0	±41.0
(n)	(9)	(9)	(9)	(9)	(9)	(9)	(9)	(9)	(9)	(7)	(9)	(9)
Total protein	5.8	3.3	6.4	2.7	1.3	0.9	5.8	6.1	2.5	0.5	15.2	18.9
(mg)	±1.6	±1.2	±1.3	±1.5	±0.4	±0.2	±2.3	±0.9	±0.7	±0.3	±6.2	±5.5
(n)	(9)	(9)	(9)	(9)	(7)	(5)	(7)	(9)	(7)	(4)	(9)	(9)
CAT	5.7	6.0	3.7	7.8	4.6		11.7	7.8	7.9		24.3	14.9
(μmol/h/g prot.)	±1.6	±1.9	±1.2	±3.3	±1.9		±5.6	±2.4	±2.4		±6.4	±6.0
(n)	(9)	(9)	(9)	(8)	(5)		(7)	(9)	(6)		(9)	(9)
GABA	58.6	64.1	27.7	34.9			64.9	43.8	53.6		74.7	71.2
(μmol/g prot.)	±14.7	±11.9	±6.4	±15.8			±8.2	±7.9	±10.9		±10.7	±13.6
(n)	(9)	(7)	(9)	(5)			(7)	(9)	(4)		(9)	(9)
GAD	43.9	49.3	14.9	42.2	38.6	38.9	59.3	39.9	44.4	60.4	67.4	47.8
(μmol/h/g prot.)	±16.8	±27.8	±7.0	±18.3	±19.8	±21.5	±29.0	±20.3	±21.3	±24.8	±39.1	±21.6
(n)	(9)	(9)	(9)	(8)	(7)	(4)	(7)	(9)	(6)	(4)	(9)	(9)
Dopamine	0.7	1.8	0.6	4.7	1.8	3.4	1.3	1.5	2.8		7.7	1.9
(μg/g prot.)	±0.6	±2.0	±0.7	±6.1	±3.3	±3.9	±0.7	±1.5	±2.6		±4.5	±0.6
(n)	(8)	(9)	(9)	(8)	(7)	(4)	(7)	(9)	(7)		(9)	(9)
Noradrenaline	16.9	20.1	2.8	11.2	11.0	3.0	16.1	12.6	9.8		9.8	10.5
(μg/g prot.)	±10.4	±11.3	±1.9	±8.7	±9.6	±0.6	±10.7	±9.2	±5.1		±6.6	±7.5
(n)	(8)	(9)	(9)	(9)	(6)	(3)	(7)	(8)	(7)		(9)	(9)
Adrenaline	0.8	1.1	0.25	0.9	1.0	1.0	0.9	0.8	0.6		0.9	0.5
(μg/g prot.)	±0.4	±0.6	±0.2	±0.4	±0.6	±0.2	±0.3	±0.5	±0.3		±0.6	±0.2
(n)	(8)	(8)	(8)	(9)	(6)	(3)	(7)	(9)	(7)		(9)	(8)

The results are expressed as mean values ± SD. (n) = number of cases assayed.

be performed in a comparable way by different workers. In this paper, the preliminary neurochemical results on the nine dissected cases were used to test the repeatability of the dissection method, by looking for consistent differences in mean concentrations between adjacent regions. The result of the student's t-test (Table 3) show that, except for the dorsomedial, paraventricular nuclei and dorsal area, all the boundaries tested separated regions with significantly different concentrations of at least one neurotransmitter or neurotransmitter-synthesizing enzyme. The method, therefore, appears to have consistently led to the dissection of the same anatomical regions in the different specimens.

TABLE 3. DIFFERENCES IN MEAN CONCENTRATION BETWEEN ADJACENT REGIONS

	Ant	*DM*	*VM*	*Post*	*Lat*
Pre	CAT***				CAT** Da**
DM	CAT*		ns		
VM	CAT**	ns		GABA*	CAT***
PV	CAT*	ns			
Lat	Adr**		CAT***	CAT**	
Ant		CAT*	CAT**		Adr**
Post			GABA*		CAT**
Inf			GABA*		GABA***
Mam				CAT***	
Dors		ns		ns	
SO					Adr**

The results of the student's t-test are shown only for pairs of regions sharing a common anatomical border. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ when at least one chemical was present in significantly different concentrations in the two regions. ns = when none of the neurotransmitters or enzymes showed a significantly different concentration between the two regions.

Analysis of the relative concentrations of the neurotransmitters and enzymes in the different regions and comparison of the results with previously published work can then give information on the accuracy of the anatomical localization of the regions.

The results of the assays were expressed per unit of protein rather than per unit wet weight as this avoids error due to the variable water content of the tissue, an increasing problem as one gets closer to the ependymal surface.

All five neurotransmitters and enzymes were measurable in all the regions assayed. In the case of dopamine and adrenaline, some of the regions had very low concentrations, but they were almost always well above the limits of sensitivity of the assay (twice the value of the blank). The average ratio of concentrations of dopamine to noradrenaline to adrenaline for the whole hypothalamus was 3:14:1.

The amount of scatter observed between cases for a given region varied considerably for the different chemicals (fig. 5 and Table 2). The contribution of pre- and post-mortem factors in this variable degree of scatter was reviewed by Spokes (1979). The results of the GABA assays had the lowest average standard deviation (22 per cent). The regional distribution of GABA and GAD were roughly in agreement, but the GAD activity, perhaps because it is more readily affected by pre-mortem factors, had an average standard deviation of 49 per cent and was less useful than GABA to compare groups of results. The results of the catecholamine assays had the widest scatter of values, probably because of their instability in post-mortem tissue and the small number of cases assayed for certain regions.

The mammillary nuclei had the lowest concentrations of all the neurotransmitters and enzymes studied.

The highest concentrations of dopamine, CAT and GABA were found in the preoptic area. High levels of dopamine were also found in some, but not all cases, in the infundibular and supraoptic nuclei and the dorsal area. There was a low but consistently measurable concentration of dopamine in all the other regions. Extensive histochemical and microdissection studies in the rat (reviewed by Hökfelt *et al.*, 1978) have shown a similarly localized distribution of dopamine. The distribution of CAT showed marked contrast between several adjacent regions, being highest in the preoptic, anterior and lateral areas, that surround the ventromedial, dorsomedial and paraventricular nuclei, which all had significantly lower CAT concentrations.

Noradrenaline and adrenaline seemed to have the reverse tendency, being high in the more centrally located nuclei and lower in the lateral (both catecholamines) and preoptic area (noradrenaline only). Of interest is the fact that the highest concentrations of both noradrenaline and adrenaline were observed in the dorsomedial nucleus, which is the region where the highest noradrenaline and second highest adrenaline concentrations were measured in the rat (reviewed by Palkovits, 1978). The dorsomedial nucleus was also where the second highest concentrations of adrenaline were found in the human hypothalamus (Mefford *et al.*, 1978) and where the highest concentrations of nerve terminals positive for PNMT (the enzyme responsible for adrenaline synthesis) were seen in the rat on immunofluorescence staining (Hökfelt *et al.*, 1978).

The ratio of noradrenaline to adrenaline was quite constant, except for three regions (supraoptic, paraventricular nuclei and preoptic area), where the noradrenaline concentrations were relatively low and the adrenaline levels remained high.

GABA was found in high concentrations throughout the hypothalamus. The posterior area and infundibular nuclei had, however, significantly lower concentrations than the adjacent ventromedial nucleus. These results agree well with the histochemical data on the rat that shows a 'dense network of GAD-positive fibres in almost all hypothalamic nuclei . . ., but considerably less in the median eminence'

(Hökfelt *et al.*, 1978). The neurochemical data is therefore compatible with a number of previously published results on animal and human material, and provides some evidence that the same anatomical regions were dissected in the different specimens.

SUMMARY

A new method was developed for the microdissection of the human hypothalamus, based on a local system of co-ordinates, using the fornix as an internal reference curve.

Dopamine, noradrenaline, adrenaline, CAT, GAD and GABA were assayed in twelve microdissected nuclei and areas, in nine human post-mortem cases. This neurochemical study was aimed to demonstrate the validity of the dissection method, and its potential usefulness for the controlled study of groups of abnormal human cases.

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THE NEUROLOGY OF VISUAL ACUITY

by L. FRISÉN

(From the Department of Ophthalmology, University of Göteborg,
Sahlgren's Hospital, S-413 45 Göteborg, Sweden)

INTRODUCTION

VISUAL acuity, or the capacity for visual discrimination of fine details of high contrast, is probably the most studied of all sensory functions. The history of quantitative measurements carries back at least to 1705, when Hooke's observations on the *minimum separabile* in the astronomical domain were published. The first more elaborate study was made by Mayer in 1754. Clinical interest in visual acuity dates back to the 1860s, spurred by Snellen's development of a widely accepted letter chart, and Donders's promotion of this chart for simultaneous determinations of visual acuity and refractive errors (*see* Donders, 1866; Snellen and Landolt, 1874).

A considerable body of knowledge exists today concerning the physiology of visual acuity (*see* Sloan, 1951; Riggs, 1965; Westheimer, 1965; Lit, 1968; Ogle, 1969; and Thomas, 1975, for excellent reviews). A vast amount of information has also been collected on disorders of the visual system associated with impaired visual acuity. Refractive errors and other optical faults have been covered extensively in standard texts (*cf.* Sloan, 1951). Much less is known about the pathophysiology of impaired acuity in retinal diseases, but dislocation, destruction, and disconnection of photoreceptors are examples of intuitively acceptable mechanisms that have just begun to receive confirmation (Fankhauser, Enoch and Cibis, 1961; Frisén and Holm, 1977; Fitzgerald, Enoch, Campos and Bedell, 1979; Frisén and Frisén, 1979; Pokorny, Smith and Johnston, 1979). Likewise, loss of acuity due to destruction of papillomacular nerve fibres at the level of the optic disc has received attention (Hayreh, 1970; Eagling, Sanders and Miller, 1974, and others). The pathophysiology of impaired visual acuity in diseases of the retrobulbar visual system has not attracted similar attention. Even encyclopædias of neuro-ophthalmology (Wilbrand and Saenger, 1904; Guillaumat, Morax and Offret, 1959; Walsh and Hoyt, 1969) carry only scattered notes on this subject. An immense number of observations on acuity levels in various disorders of the retrobulbar visual system is available in the literature but an exhaustive review is neither practicable, nor rewarding: many older reports are of mainly historical interest. Even the modern literature contains a great deal of conflicting information.

For instance, Laibovitz's (1979) impression that visual acuity may remain normal in compression of the optic nerve has been contested by Glaser and Trobe (1979). The traditional emphasis on impaired acuity in chiasmal syndromes (Wilbrand and Saenger, 1904; Cogan, 1966; Huber, 1977) is not immediately reconcilable with Cushing's (1930) finding of normal visual acuity in a patient subjected to median sectioning of the chiasm. Bender and Bodis-Wollner (1978), and Savino, Paris, Schatz, Orr and Corbett (1978) have held a severe impairment of visual acuity typical of optic tract lesions in spite of previous reports to the contrary (Lauber, 1927; Freusberg, 1938; Hoyt and Kommerell, 1973). Even the effects of occipital lobectomy on visual acuity are open to discussion (*see* Dubois-Poulsen, Magis, de Ajuriaguerra and Hécaen, 1952; Huber, 1970). Although part of the discrepancies may be attributed to varying combinations of pathogenetic mechanisms in different clinical materials, a considerable part has to be attributed to vague definitions of what is normal and abnormal.

The traditional view that 1.0 (or 6/6, or 20/20) represents normal visual acuity was already strongly refuted by Snellen and Donders: even Mayer (1754) obtained considerably better results. The 1.0 level actually borders on the lower extreme of findings in normal individuals (*see* Chapanis, 1950, for a well controlled study). Nevertheless, clinicians often tend to push the lower limit of normal below 1.0. The World Health Organisation (1973) does not recognize visual impairment until acuity has dropped below 0.3 or 20/70! The frequently arbitrary decisions of various investigators regarding lower limits of normal may be a consequence of the quite arbitrary scaling of acuity charts (*see* Westheimer, 1979, for a recent review). A scale based on a relationship between structural and functional changes remains to be constructed. A recent study by Frisén and Frisén (1979) gives some insight into loss of acuity in terms of structural changes. Their findings in patients with abnormal photoreceptor separations predict that a normal neural substrate should allow approximately 1.5 (20/13) acuity, but 1.0 (20/20) requires no more than 44 per cent of the normal complement of foveocortical neural channels, and 0.3 (20/70) no more than 5 per cent. (A neural channel is here defined as an independent pathway for signal transmission, which connects a foveolar cone with the visual cortex.) These predictions fit with experimental observations obtained in the rhesus monkey by Tso, Robbins and Zimmerman (1974).

The present report gives the results of conventional acuity tests in a series of cases with reasonably well defined lesions of various parts of the visual pathways. The results indicate that an acuity level below 1.0 never should be accepted as normal: acuity is usually considerably better in normal individuals. Cogan's (1966) dictum that disorders of the retrochiasmal visual pathway never impair acuity (unless there are bilateral lesions) has been corroborated. Lateral chiasmal lesions typically produce impaired acuity in the ipsilateral eye. Mid-chiasmal lesions regularly lead to impaired visual acuity in both eyes, roughly in proportion to the extent of the field defect. A subnormal visual acuity is a common finding also in patients with visual field defects apparently restricted to the temporal fields.

Likewise, compression optic neuropathy is regularly associated with a subnormal acuity in the involved eye. Hence, acuity appears to remain normal (= 1.0, or better) as long as either the crossing or the non-crossing outflow from the retinal foveola remains intact: acuity fails only when both crossing and non-crossing outflows are compromised. Acuity tests appear to be more sensitive than perimetric tests for detecting such conditions.

PATIENTS AND METHODS

The patients reported in this study were all inpatients at the Department of Neurosurgery. They were carefully selected in many respects. The two most important requirements were an unimpaired ability to participate in the examinations described below, and the presence of well defined lesions. Patients with high ametropia, cloudy media, pupillary abnormalities, nystagmus, facial palsy, or other conditions potentially capable of influencing the test results were rejected from the study. Further details will be given below.

Every patient was subjected to a careful neuro-ophthalmological work-up using standard clinical tools under constant conditions. Monocular visual acuity was determined with the best correction, using Donders's (1866) procedure. An officially approved acuity chart (KIFA: Monoyer-Granström) with black *sans serif* letters on a white background was illuminated with 1,000 lux from white fluorescent tubes in a LIC Universal light box. The room illumination adjacent to the chart was approximately 200 lux. These illumination levels ensure optimum results (Aulhorn 1964). The test distance was 5 m. The chart contained the following optotype sizes in decimal notation: 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, 1.0, 1.5 and 2.0. Each eye's acuity level was taken as the finest optotype line where 75 per cent, or more, of the optotypes were correctly identified. There was no time limit. The refractions were carried out to the nearest 0.25 diopters (*cf.* Campbell, 1957). All measurements were made with the natural pupil (*cf.* Campbell and Gregory, 1960). In a few instances, determinations of acuity for sinusoidal gratings were also made (*see* Frisén and Frisén, 1979, for details).

Each patient was subjected to several tests of peripheral vision. These included confrontation tests of peripheral limits and symmetry of paracentral colour saturation (Frisén, 1973*a*), and kinetic perimetry in the Haag-Streit Goldmann 940 ST instrument as outlined elsewhere (Frisén, 1979*a*). These tests were sometimes supplemented by static perimetry within selected areas. The perimeter's fixation-monitoring telescope was replaced with a television system giving 4 × magnification to improve control of fixation. Corollary examinations were sometimes made at the tangent screen using targets of fixed angular subtense and variable luminance, and 2 m test distance (Frisén, 1974). Appropriate corrections for refractive errors and presbyopia were always used.

Special attention was paid to the appearance of the peripapillary retinal nerve fibre layer, a useful indicator of the state of the anterior visual pathway (*see* Hoyt, 1976; Frisén, 1979*b*, for reviews). The evaluations were mostly made in direct ophthalmoscopy, using red-free light. Fundus photography was occasionally used for the same purposes. Further details will be given below.

All examinations were made by the author.

RETROBULBAR OPTIC NERVE LESIONS

Clinical experience dictates that loss of visual acuity is highly characteristic of optic neuropathies, irrespective of the actual cause (*see* Walsh and Hoyt, 1969, for an extensive survey). In fact, the incidence of impaired acuity is so high that it may be proper to inquire whether there exists any form of acquired optic nerve lesion that with notable frequency spares the papillomacular bundle. Pathoanatomical confirmation of such an exception seems to be restricted to one form of so-called tabetic optic atrophy (Bruetsch, 1953; Lindenberg, Walsh and Sacks, 1973). Strictly peripheral loci of demyelination (Chamlin, 1953), and occlusion of superficial branches of the pial vascular supply of the optic nerve (Hughes, 1958; Hayreh, 1970), are examples of other disorders that have been held capable of sparing central vision, although the expectations as yet seem to be unconfirmed. Perimetric evidence of so-called sparing of fixation is insufficient evidence of sparing of foveolar vision because of the imperfect correlation between simple contrast sensitivity, as tested in perimetry, and visual acuity (*cf.* Best and Bohnen, 1955; Aulhorn, 1964, 1978).

The question whether so-called compression optic neuropathy ever spares visual acuity is of particular interest in clinical work. Among recent writers, Laibovitz (1979) and Glaser and Trobe (1979), appear as proponents of different views. However, a definitive answer to this question is difficult to obtain from simple clinical observations. Mere co-existence of a visual field defect and a mass lesion adjacent to the optic nerve does not prove a causal relationship: the field defect may very well have an unrelated ætiology. Low-degree optic nerve hypoplasia may be cited as an example of a not infrequent coincidental cause of field defects that may be difficult to diagnose correctly (Frisén and Holmegaard, 1978). Improved insight seems to require either analysis of the mode of progression in individual cases, or analysis of several cases with different severity of compression optic neuropathy.

Opportunities to analyse modes of progression are very rare, and only one single case appears to have been studied in detail. Frisén, Sjöstrand, Norrsell and Lindgren (1976) described a patient with an infra-optic craniopharyngioma cyst, where the cyst could be drained to the exterior through a fine, indwelling catheter. More than 50 cycles of cyst filling and drainage were monitored by visual function tests. An important observation made in this unique case was that a change in the visual field was always preceded by a drop of acuity.

Analysis of several cases with different severity of compression optic neuropathy poses several difficulties, particularly with regard to definition of the severity of compression. Assessment of the degree of compression from surgical findings is probably practically impossible. Visual field changes are more easily accessible to quantification, but their relationship to the severity of compression is poorly understood. There are several indications that ordinary perimetry leaves something to be desired with regard to detection of a diffusely distributed loss of visual pathway neurons (Frisén, 1979*a*, *b*; *see also below*).

An alternative way of obtaining information on the severity of optic nerve compression involves radiological assessment of the area of the optic canal in diseases causing optic canal stenosis:

Present Investigation

A possible relationship between the degree of optic canal stenosis and visual acuity was sought in a series of patients with unilateral meningioma of the medial sphenoid wing. Fifteen cases with this diagnosis were available for review. Seven patients had to be rejected because of radiological or surgical evidence of globular meningioma components capable of compressing the optic nerve outside the canal, or proptosis of such a degree that it caused corneal exposure or impaired motility. Eight cases without such complications, and a diagnosis of pure *en plaque* meningioma, remained for analysis. Their ages ranged between 29 and 66 years (average 48); seven were females. Pre-operative axial radiographs of the optic canals were retrieved and the luminal areas of the canals were determined from the films. The relative reduction of area on the side of involvement was plotted against visual acuity (fig. 1). The relationship between the degree of canal stenosis and visual acuity was loosely defined: the product moment correlation coefficient equalled −0.63. Nevertheless, it is interesting to note that the extrapolation of the least squares regression line to zero reduction of area intersects the acuity axis close by the 1.0 level.

Acuity in the contralateral eye was 1.0 in six instances, and 1.5 in one. One eye was amblyopic since childhood.

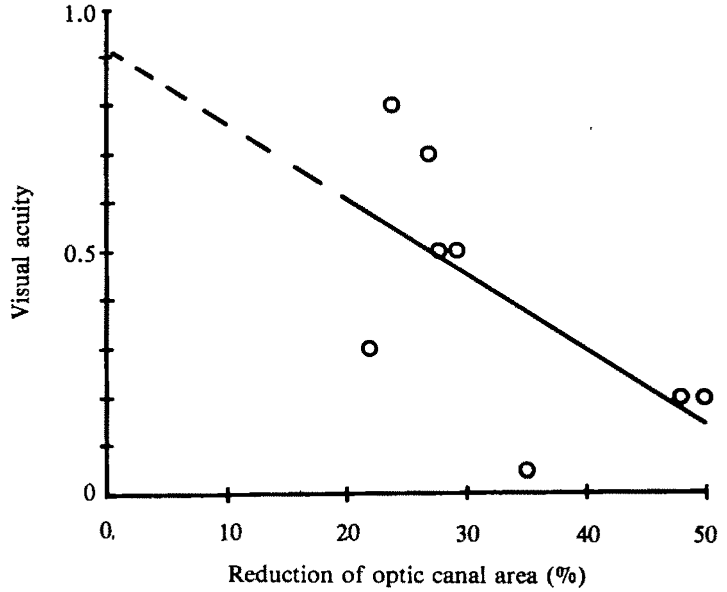

FIG. 1. Relationship between acuity level and reduction of optic canal area (relative to normal side) in 8 cases of medial sphenoid wing meningioma. Correlation coefficient −0.63. Note that the extrapolation of the least squares regression line intersects the acuity axis close by the 1.0 acuity level.

Comment

The emphasis in the contemporary clinical literature (*see* Knight, Hoyt, and Wilson, 1972; Trobe and Glaser, 1978) on impaired visual acuity as an early sign of compression optic neuropathy appears to be well grounded. The degree of acuity impairment also appears to be a useful indicator of the severity of compression (fig. 1). A simple measurement of acuity may be even more informative than attempts to assess the state of the papillomacular bundle by ophthalmoscopy, or perimetry. A relationship has been observed between the level of visual acuity and the ophthalmoscopic appearance of the intraocular part of the papillomacular bundle in clinically diagnosed optic neuropathies (Tagami, 1979), but acuities of 1.0 or better were encountered in several patients with a considerable degree of atrophy. This discrepancy arises from the fact that the integrity of the fine-calibre nerve fibres serving the retinal foveola cannot be ascertained with presently available optical aids (Frisén, 1973*b*). The more massive non-foveal nerve fibre bundles are easier to evaluate. An extensive loss of axon bundles is usually required before perimetry becomes abnormal. Enoksson and Johansson (1978) have presented a particularly instructive series of cases with altitudinal field defects due to optic nerve lesions, where ostensibly normal parts of the visual field were served by parts of the retinal nerve fibre layer which appeared to be nearly as severely affected as those corresponding to the field defects.

Concerning acquired optic neuropathies from causes other than compression, there is little or no proof available that acuity may be spared with the exception of one variant of tabetic optic neuropathy, rarely encountered today (Bruetsch, 1953).

The very high incidence of disturbances of central vision in optic neuropathies has long been ascribed to a selective vulnerability of papillomacular nerve fibre bundles. This vulnerability has been attributed to various factors, including a high metabolic demand of the tightly packed fine-calibre axons (Potts, Hodges, Shelman, Fritz, Levy, and Mangnall, 1972), and an easily disturbed capillary circulation (Lindenberg and Walsh, 1964). The receptive field organization of the retina suggests an alternative explanation for an early impairment of visual acuity. The 100-fold discrepancy in number between retinal input cells (rods and cones) and output cells (ganglion cells) forces the convergence of several receptors on one and the same ganglion cell, and the formation of receptive fields. The diameters of receptive fields are held to increase with increasing eccentricity in the retina. There is also extensive overlapping among receptive fields, except in the fovea. Here, the cones are held to have one-to-one connections with their own ganglion cells (*see* Polyak, 1957, for references). Against this anatomical background, it appears likely that the peripheral visual field may be upheld with a severely reduced number of ganglion cells whereas foveolar acuity fares poorly in the same situation.

There is no evidence of redundancy in the optic nerve as far as visual acuity is concerned. On the other hand, there appears to be considerable redundancy, or an appreciable 'margin of safety', with respect to perimetry, and, although to a lower degree, to ophthalmoscopic evaluation of the retinal nerve fibre layer (Enoksson and Johansson, 1978; Frisén, 1979*a*, *b*). The frequently alleged superiority of novel tests of central vision will be brought up in the Discussion section.

CHIASMAL LESIONS

Impairment of visual acuity due to a chiasmal lesion had been observed already by Müller (1861), who published the first clinicopathological study. Müller's findings have been amply confirmed by later investigators, for example, Cushing and Walker (1915), de Schweinitz (1923), Traquair (1949), and Tagami, Hiramatsu, and Isayama (1979). A relationship between the level of acuity and the extent of the visual field defect is suggested in the staging schemes proposed by Cushing and Walker (1915) and Wilson and Falconer (1968). However, only Tagami, *et al.* (1979) appear to have attempted a closer analysis. These investigators were unable to define a relationship between visual acuity and perimetric sparing of fixation. As indicated above for the optic nerve, grading of the extent of visual field defects is a debatable measure of the severity of visual pathway lesions. Parallel studies of the degree of atrophy of the retinal nerve fibre layer, and the perimetric extent of visual field defects, have indicated that visual field defects often lag behind signs of structural damage in patients who have been operated on for pituitary adenomata (Lundström and Frisén, 1976). Nevertheless, perimetry and ophthalmoscopic evaluation of the state of the retinal nerve fibre layer presently appear to be the only universally available techniques for gauging the extent of chiasmal lesions. In the present context, ophthalmoscopy has the poorer potential because of the difficulty of visualizing the fine-calibre axons serving the retinal fovea: this technique is better suited for pre-operative assessment of the reversibility of visual field defects (Lundström and Frisén, 1976, 1977). Perimetry, therefore, is the only remaining method. Estimation of the severity of a chiasmal lesion from the appearance at surgery is probably practically impossible.

Present Investigations

Amongst the many causes of chiasmal lesions encountered in clinical practice, so-called compression of the optic chiasm by an adjacent mass appears to offer the best possibilities for a study of the pathophysiology of visual acuity. The files of all cases operated for such mass lesions at the Department of Neurosurgery from 1974 to 1979 were reviewed. Only patients who had been able to participate in the full examination programme described above were retained for further analysis. Fifty patients remained after deleting those with complicating conditions capable of influencing visual functions. Only pre-operative measures of vision were used to ensure freedom from surgical or radiotherapeutic complications.

The complicated arrangement of nerve fibre bundles in the chiasm, still incompletely understood, and the varying relationships between the chiasm and the suprasellar mass explain the large variety of visual field defects encountered in clinical practice (Hoyt, 1970; Hollenhorst and Younge, 1973; O'Connell, 1973). However, it is usually simple to distinguish two major types, *viz.* more or less median chiasmal lesions and lateral chiasmal lesions. Such a subdivision was made in the present material on the basis of the visual field records: all patients with visual field defects considered to belong to the bitemporal family were referred to a median group, and all others to a lateral group. Another median/lateral subdivision was based on the findings at operation, which was transcranial in all instances. The two methods of subdivision gave precisely the same results. The median lesion group contained 40 cases (average age 44 years, range 16–71 years), and the lateral lesion group 10 cases (average age 45, range 19–62 years). There were 35 cases of pituitary adenoma and 5 of craniopharyngioma in the median group. The lateral group comprised 4 large ophthalmic artery aneurysms, 3 pituitary adenoma, one craniopharyngioma, one myxochondroma and one middle fossa meningioma.

TABLE 1. SCORING OF VISUAL FIELD DEFECTS

*Perimetric defect**	*Score*
Relative defect in 1 quadrant	1
Relative defects in 2 quadrants or an absolute defect in 1 quadrant	2
Absolute defects in 2 quadrants	3
Relative or absolute defects in 3 quadrants	4
More than 3 quadrants affected	5

* An absolute defect is arbitrarily defined as a defect delineable with the V4 stimulus of the Goldmann perimeter. All other defects are labelled relative.

The visual field defects were scored separately for each eye on the basis of isopter deformations (Table 1), deliberately disregarding the conditions in the very centre of the field. Exclusion of the very centre of the field is appropriate under the present circumstances where severity of compression is the independent variable, and central visual acuity is the dependent variable.

For visual field defects belonging to the temporal family, scores 1–3 reflect perimetric evidence of disturbed conduction in nerve fibres which cross in the chiasm, while the higher scores reflect disturbed function also in non-crossing fibres. The two main types of visual field abnormality typically encountered in chiasmal compression, *viz.* depressions and scotomata (*cf.* Wilson and Falconer, 1968; Sugita, Sato, Hirota, Tsugane and Kageyama, 1975) were graded in the same way. Each eye was scored separately. There were no instances of hemianopic temporal arcuate scotomata in the present series (*see* Trobe, 1974).

Results

The relationship between visual acuity and the severity of the visual field defect in the median lesion group is shown in fig. 2. Each patient is represented by two symbols, one for each eye. The relationship is rather poorly defined because of considerable variation. However, all eyes with perimetric evidence of disturbed conduction in both crossing and non-crossing nerve fibres (visual field score $\geqslant 4$) had a subnormal acuity (< 1.0). Importantly, a subnormal visual acuity was also of frequent occurrence in eyes with perimetric signs of disturbed conduction only in crossing fibres: a subnormal acuity was found in no less than 19 out of 40 eyes with a field defect scoring 2. Patients with depression-type visual field defects and patients with scotomatous field defects appeared to behave similarly with regard to acuity loss (fig. 2).

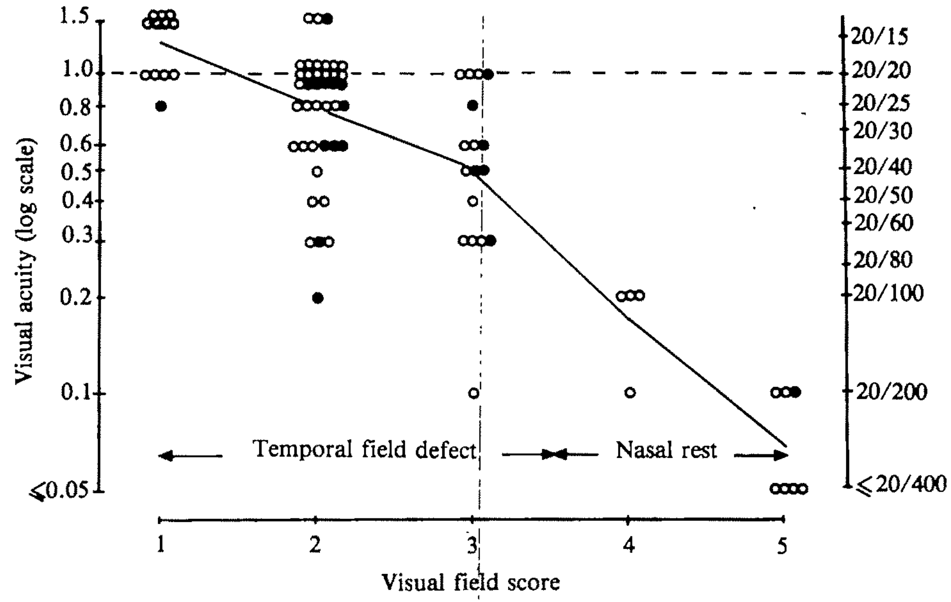

FIG. 2. Relationship between log acuity level and severity of visual field defect in 40 cases with median chiasmal lesions. ○ symbolizes eyes with depression-type visual field defects, and ● eyes with scotomatous defects. Interrupted line identifies lower limit of normal acuity, and solid line connects geometric average acuities for each visual field score. For definition of scores *see* Table 1 and text.

Evidence that even an acuity level of 1.0 may be subnormal was furnished from post-operative observations: 8 eyes with a pre-operative visual acuity of 1.0 improved to 1.5 after operation.

Out of the 40 patients in the median lesion group, 20 obtained the same visual field score in both eyes. Considerable asymmetry was still more common than indicated by this number, however. Only 5 patients showed quite symmetrical visual field records; 8 had symmetrical acuities.

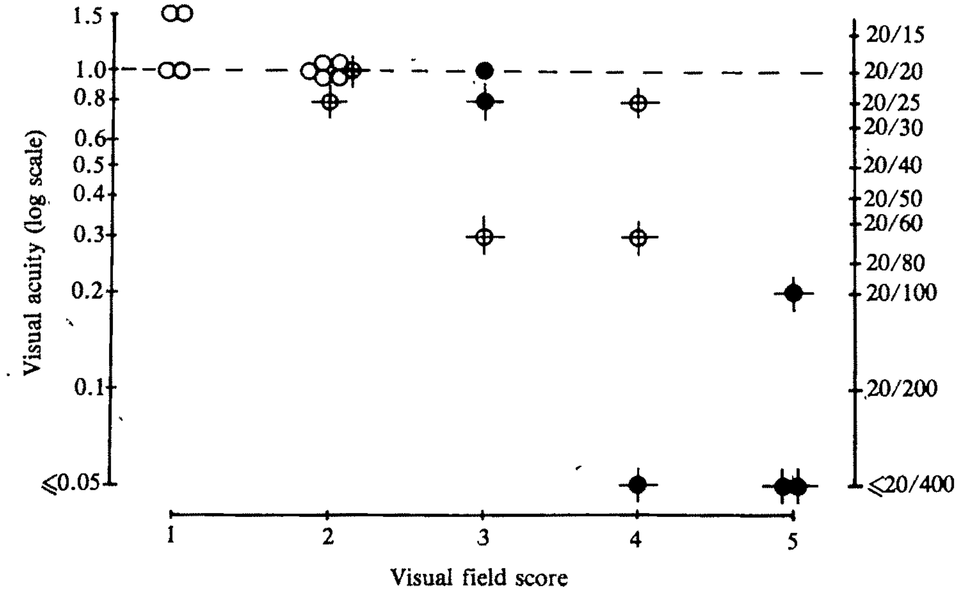

FIG. 3. Acuity levels in 10 cases with lateral chiasmal lesions. + identifies eyes ipsilateral to the responsible lesion. *See legend* to fig. 2 for definition of other symbols.

The relationship between visual acuity and the severity of the visual field defect in the lateral lesion group is illustrated in fig. 3. Each patient is represented by two symbols, one for each eye. The eye on the side of the lesion had a subnormal visual acuity (< 1.0) in all cases but one. The contralateral eyes all had a normal visual acuity ($\geqslant 1.0$). The pattern of field loss was highly variable. There were 3 instances of homonymous and congruous visual field defects, 2 of homonymous and incongruous visual field defects, and 5 of anterior knee syndromes. The latter 5 all had severely depressed functions in the ipsilateral eye suggesting optic nerve compression, and a low degree (score 1-2) temporal defect in the contralateral eye, with a full periphery. Three of these patients had giant ophthalmic artery aneurysms, one had a pituitary adenoma with a lateral cupola, and one had a middle fossa meningioma. The 5 instances of homonymous defects were due to pituitary adenomata (3 cases), a craniopharyngioma, and a middle fossa myxochondroma, respectively.

Two patients with a pre-operative visual acuity of 1.0 in the eye contralateral to the lesion improved acuity in this eye to 1.5 after operation.

Comment

In spite of the uncertainties inherent in perimetric estimates of the severity of chiasmal lesions, there seems to exist reasonably consistent relationships between the site and severity of the lesion, as assessed by perimetry, and visual acuity. In *median* chiasmal syndromes, acuity failed progressively with increasing field defects. A distinctly subnormal acuity was seen in about 50 per cent of cases with visual field defects scoring 2, while the incidence was 100 per cent when the field defects scored 4 or higher. There was no correlation between the level of acuity and the position of the chiasm in relation to the tumour. These results speak forcefully against a well defined position within the chiasm of macular nerve fibres, in keeping with findings in experimental animals (Polyak, 1957; Hoyt and Luis, 1963).

The pattern of acuity loss is different in *lateral* chiasmal syndromes: in the present series acuity was subnormal in at least 9 out of 10 ipsilateral eyes, and normal in all contralateral eyes. The different fate of acuity in median and lateral syndromes can be explained in terms of the nerve fibre arrangement in the chiasm (*see* Polyak, 1957; Hoyt, 1970; O'Connell, 1973). A lateral compression of the chiasm will tend to affect both crossing and non-crossing fibres from the ipsilateral eye, but predominantly crossing fibres from the contralateral eye. The present observations therefore suggest that acuity remains normal if the non-crossing set of foveal fibres remains unaffected. Support for this interpretation comes from Cushing's (1930) report of retention of normal visual acuity following median sectioning of the chiasm. As will be shown below, patients with pure homonymous hemianopias have a normal acuity in both eyes. Hence, acuity will remain normal if either the crossing or the non-crossing set of nerve fibres from the fovea remains intact, and acuity will fail only when both sets of foveal fibres are affected.

A simultaneous involvement of both sets of foveal fibres from one and the same eye is obviously of common occurrence in *median* chiasmal lesions. Here acuity often fails long before the appearance of perimetric signs of impaired function in the nasal visual field (fig. 2). It may therefore be assumed that the severity of the lesion in compression of the chiasm is often much greater than reflected by perimetry. The reasoning is supported by the frequent divergence of results of nerve fibre layer evaluation and perimetry: vision, as tested by perimetry, is frequently better than expected from the degree of atrophy in steady state patients (Lundström and Frisén, 1976). It appears that a substantial reduction of the neural substrate is required before perimetry can detect a functional impairment: the perimetric test situation appears to put small demands on the visual system. Related observations have frequently been made by neurosurgeons, who, when seeing the extent of chiasmal deformation at operation, would often have expected a much larger functional deficit (Cushing and Walker, 1915, and others). The poor sensitivity of perimetry for detecting a diffusely distributed drop-out of neural channels is particularly striking in cases with severely deformed chiasms, where careful perimetry has occasionally shown ostensibly normal results (Cushing and Walker, 1915; Möller and Hvid-Hansen, 1970). It may be that a perimetric test demanding more than mere detection, for example, some kind of *minimum separabile* discrimination, would have superior sensitivity (Frisén and Frisén, 1977).

Supraliminal tests of colour saturation also appear to offer improved sensitivity, although the possibilities of quantification are limited (Frisén, 1973*a*; Dannheim, 1977).

Attempts toward a more precise topographical analysis of visual field records appear ill advised because of the large size, in relation to the chiasm, of the ordinary suprasellar mass at the time of clinical presentation (*see* Adler, Austin and Grant, 1948). Another argument for clinical recognition of only two chiasmal syndromes comes from the generally poor knowledge in the individual case concerning the position of the chiasm. Autopsy studies of cases without suprasellar masses indicate an incidence of a postfixed position of the chiasm of 4 to 15 per cent (Schaeffer, 1924; Renn and Rhoton, 1975), but the situation is quite different in patients with suprasellar lesions. No less than 47 per cent of the patients reviewed here were thought to have acquired postfixation of the chiasm at operation. A high incidence of acquired postfixation has been reported also by Wilson and Falconer (1968). The scotomatous variant of bitemporal field defects is often attributed to a prefixed position of the chiasm (Jefferson, 1940, and others). However, out of the 8 patients with such defects reviewed here only 2 were found to have prefixed chiasms at operation: 2 had postfixed chiasms. The explanation for scotomatous defects must obviously be more complicated. Any hypothesis for their production must be able to explain why a patient may have a depression-type defect in one eye and a scotomatous defect in the other (this situation was encountered in 6 of my patients), and also why a scotomatous defect may change to a depression-type defect, or *vice versa*, post-operatively (such changes in the nature of the defect occurred four times in the present series). The rate of development of chiasmal compression and the degree of angulation of the optic nerve, may be factors of importance (*see* Sugita *et al.*, 1975).

So-called anterior knee syndromes are classically held to depend on the formation of loops of nerve fibres in the optic nerve from the contralateral eye (Traquair, 1949; Polyak, 1957; Bird, 1972). Such loops seem to occur primarily in cases where the optic nerve joins the chiasm at an acute angle (Hoyt and Luis, 1963; Hoyt, 1970). The same combination of visual defects can probably be produced also in cases lacking looping nerve fibres, for example, by an eccentric prechiasmal mass impinging both on the middle of the chiasm and on one optic nerve. Therefore, the topical implications of anterior knee syndromes may be quite vague in reality. Hence, it appears logical to subdivide the chiasmal compression syndromes into median and lateral varieties only as done here. Sequestration of an anterior knee syndrome has merit primarily with regard to ætiology: this syndrome is rarely caused by a pituitary tumour (*see also* Bird, 1972).

Finally, it should be stressed that even midline suprasellar masses rarely affect only the chiasm. Displacement of one or both optic nerves, or one or both optic tracts, is nearly universal. The chiasm may well bear the brunt of damage in many instances but the term 'chiasmal compression' is too simplistic to reflect actual conditions in most cases. Furthermore, the pathophysiology of conduction failure in 'compression' is poorly understood (*see* Hoyt, 1970; O'Connell, 1973; Frisén *et al.*, 1976). The term compression merits use primarily for convenience.

OPTIC TRACT AND LATERAL GENICULATE LESIONS

Lesions of the optic tract and the lateral geniculate body are often difficult to differentiate from suprageniculate lesions on the basis of traditional neuro-ophthalmological symptoms and signs. Most patients with retrochiasmal anterior pathway lesions seem to develop complete homonymous hemianopias fairly rapidly: opportunities to observe the classical incongruity of early stages come rarely. The apparently rapid evolution is probably a consequence of the restricted mobility of these structures and their small cross-sectional areas. Under these conditions, even a small change in the size of an adjacent mass may fairly abruptly change the situation from a marginal disturbance of conduction to total failure. The small size and the protected position of these structures also tend to defeat attempts toward direct radiological demonstration of a lesion. These factors combine to make recognition *in vivo* of optic tract and lateral geniculate lesions a rather rare event. The true incidence is presumably much higher than that reflected by the paucity of clinical reports. Optic tract and lateral geniculate lesions are not rare in patients who have died from tentorial herniation (Sunderland, 1958; Lindenberg and Walsh, 1964; Lindenberg *et al.*, 1973). The same autopsy studies have also shown a high incidence of damage to the visual cortex (*see also* Hoyt, 1960). Therefore, knowledge of prior uncal herniation in surviving patients cannot be used to differentiate between an infrageniculate and a suprageniculate cause of homonymous hemianopia. The novel tool of ophthalmoscopic evaluation of the state of the peripapillary retinal nerve fibre layer offers a possibility for distinguishing between anterior and posterior visual pathway lesions: the characteristic pattern of homonymous, hemi-optic atrophy appears only with anterior pathway lesions, at least in adults (*see* Hoyt, 1976, and Frisén, 1979*b*, for reviews). Atrophy is usually complete by six weeks after infliction of the damage. The ophthalmoscopic picture is the same in patients with optic tract lesions (Lauber, 1927; Freusberg, 1938; Hoyt and Kommerell, 1973), and in lateral geniculate lesions (Hoyt, 1975). Partial damage of the lateral geniculate body (or more precisely, its dorsal nucleus) produces less extensive changes in the retinal nerve fibre layer, in keeping with the less extensive field defects (Frisén, Holmegaard and Rosencrantz, 1978; Frisén, 1979*c*). All the patients described by these investigators had pure homonymous visual field defects and visual acuities of 1.0 or better in both eyes. These findings contrast with those recently reported by Bender and Bodis-Wollner (1978), and Savino, Paris, Schatz, Orr and Corbett (1978). These latter investigators found distinctly subnormal visual acuity in at least one eye in the overwhelming majority of their cases. A review of additional patients therefore may be motivated.

Present Investigations

Seven patients with acquired, absolute, homonymous visual field defects splitting the macula, and corresponding hemi-optic atrophy, were studied. Two of these may merit closer description:

Case K.S. A 23-year-old male suddenly noticed a visual field defect homonymous to the left. On admission to the hospital, he was found to have a low-degree left hemiparesis and a trace of a left facial palsy of the central type. There was an incongruous, partly absolute, visual field defect homonymous to the left (fig. 4).

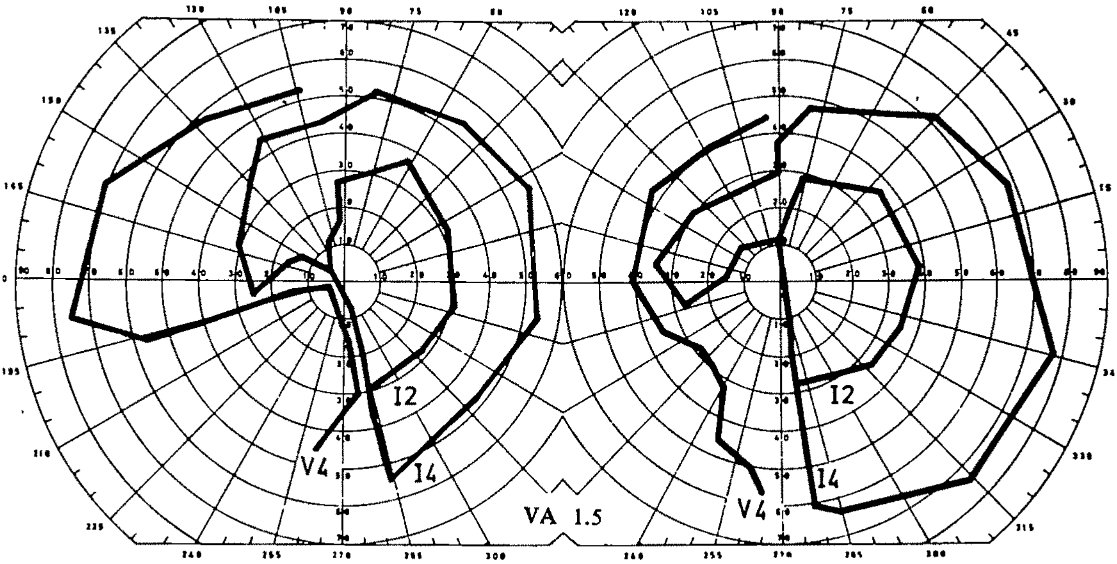

FIG. 4. *Case K.S.* Visual field defects due to a right lateral geniculate body glioblastoma. Test targets given in Goldmann designation. VA = visual acuity.

Visual acuity was 1.5 bilaterally. There was neither papillœdema nor optic atrophy. Computed tomography revealed a lesion 3 cm in diameter centred on the right lateral geniculate body (fig. 5). At operation, the tumour (a glioblastoma multiforme) was seen to infiltrate the posterior hippocampus. The tumour was partly excized. Post-operatively, the patient had a more severe left hemiparesis and a complete homonymous hemianopia to the left. Visual acuity remained at 1.5 bilaterally. Two months later funduscopy revealed the typical picture of homonymous, hemi-optic atrophy.

Acuity for sinusoidal gratings was determined three months after operation. The 50 per cent threshold was 44±2 (SD) cycles/degree in both eyes, i.e. average normal (Frisén and Frisén, 1979).

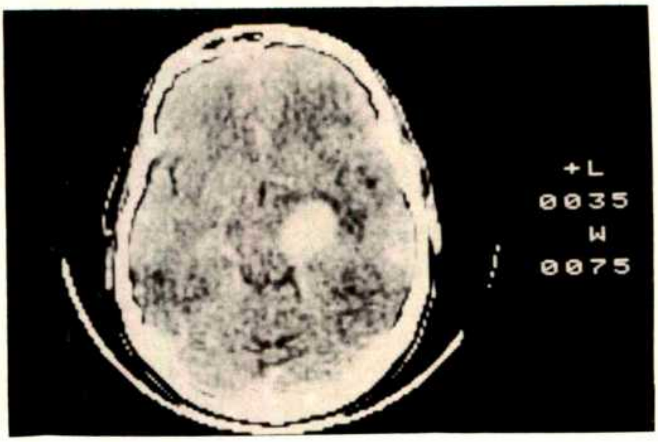

FIG. 5. *Case K.S.* Computed axial tomography shows a glioblastoma multiforme in the region of the right lateral geniculate body.

Case B.S. A 21-year-old male became aware of a left homonymous visual field defect after a traffic accident. He had no other symptoms. At the first examination, he had a complete, macula-splitting hemianopia homonymous to the left, with corresponding hemi-optic atrophy. There were no other neuro-ophthalmological abnormalities. Visual acuity was 1.5 bilaterally. Radiological examinations revealed a mass lesion centred on the right lateral geniculate body. Treatment was refused. Over the following three years there was gradual development of a central facial palsy on the left and a subtle hemiparesis on the same side. There were no changes in his neuro-ophthalmological status.

Acuity for sinusoidal gratings was 45 ± 2 cycles/degree on the right, and 44 ± 2 on the left.

Additional observations were obtained from 5 other patients, with ages ranging between 22 and 46 years (median 25 years). All but one were males; all had a visual acuity of 1.0 in both eyes. One patient with a giant carotid aneurysm pointing backwards and upwards was believed to represent a pure anterior optic tract lesion. He had a complete homonymous hemianopia. He was not explored transcranially. Two patients were considered to have vascular lesions of the posterior part of one lateral geniculate body (or more precisely, its dorsal nucleus), producing homonymous, horizontal sectoranopia with corresponding optic atrophy. The diagnosis was supported by angiography in one case, and computed tomography in the other. Both have been described in detail elsewhere as examples of the posterior choroidal artery syndrome (Frisén, *et al.*, 1978). Another 2 patients were diagnosed as probable posterior tract or lateral geniculate lesions on clinical grounds only. Both patients had homonymous hemianopia when awakening after operation for a frontal lobe arteriovenous malformation, and a subdural hæmatoma, respectively. Pre-operative examinations of vision were not possible in these two patients, who both had signs of progressive tentorial herniation on arrival at the hospital. Both later developed homonymous hemi-optic atrophy.

Case V.W., a 45-year-old male, with a presumably *bilateral* lesion of the retrochiasmal anterior visual pathway had impaired visual acuity bilaterally. He had a frontal lobe arteriovenous malformation. The pre-operative neuro-ophthalmological examination revealed no abnormality. Following operation, recovery was unremarkable until the patient developed a grand mal seizure. After this he had a right third nerve paralysis and the visual field defects shown in fig. 6. Visual acuity dropped to 0.8 in both eyes, and remained at this level during two years of follow-up. Severe bilateral optic atrophy developed about two months after the seizure, at which time the third nerve lesion had cleared. The most likely cause of the visual pathway lesions was thought to be spontaneously reversible transtentorial herniation (Sunderland, 1958; Lindenberg and Walsh, 1964), with infarction of the posterior choroidal artery territories in the lateral geniculate bodies (Frisén *et al.*, 1978).

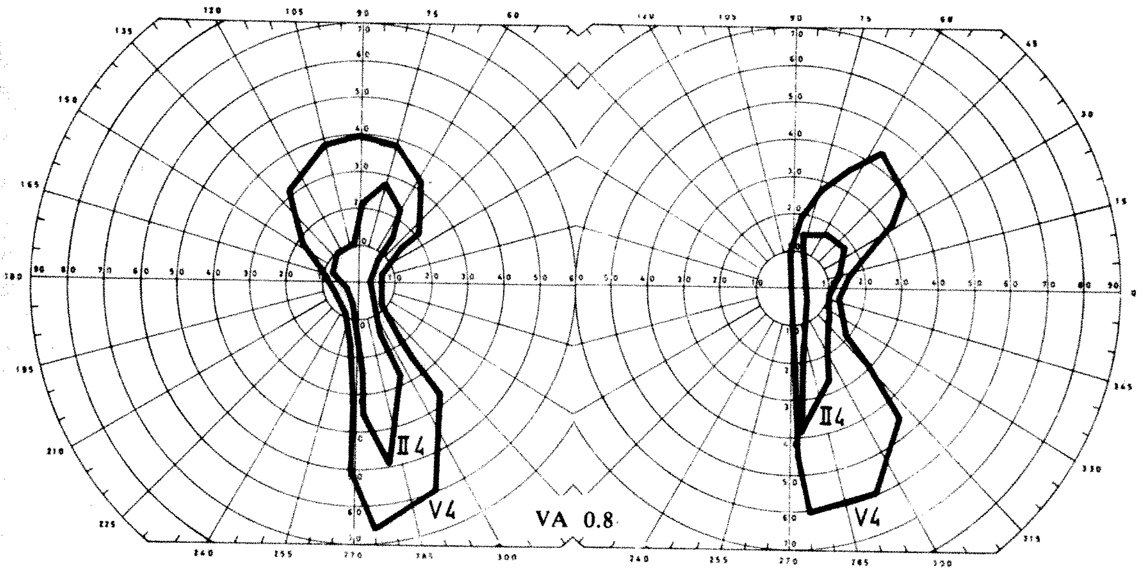

FIG. 6. *Case V.W.* Visual field defects believed to be due to bilateral lesions of the posterior optic tracts or the lateral geniculate bodies. There was corresponding optic atrophy. Note symmetrical impairment of visual acuity.

Comment

The present observations support the findings of several previous investigators concerning bilateral sparing of visual acuity with lesions presumably located to one optic tract or one lateral geniculate body. In turn, these findings support the hypothesis elaborated above, that acuity remains normal as long as either the non-crossing or the crossing outflow from the retinal fovea remains intact. These findings of bilaterally equal acuity suggest that the numbers of nerve fibres serving nasal and temporal halves of the fovea are approximately equal. The ratio of crossed to uncrossed nerve fibres in the optic chiasm is about 53:47 (Kupfer, Chumbley and Downer, 1967). It is likely that the majority of the excess of crossing fibres is destined for the peripheral retina because of the larger size of the temporal half of the visual field. The number of retinal ganglion cells is also higher in the nasal than the temporal hemiretina (van Buren, 1963).

It is interesting to consider what should happen to visual acuity if a patient with a complete homonymous hemianopia acquires another retrochiasmal visual pathway lesion on the previously intact side. There seem to be three alternatives:

(a) if the new lesion spares the foveal nerve fibres, nothing should happen to foveolar vision;
(b) if the new lesion destroys the foveal nerve fibres, foveal vision should be lost;
(c) if the new lesion destroys part of the foveal nerve fibres, acuity should be subnormal, and, in view of the apparently close apposition of foveal nerve fibres from the two eyes throughout the retrochiasmal visual pathway, acuity should be impaired to the same degree in both eyes.

Hence, bilateral lesions of the retrochiasmal visual pathways apparently need not be symmetrical to produce a symmetrical impairment of visual acuity. Case V.W. (fig. 7) supports this conclusion. Symmetrical amblyopia was also reported by Merren (1972) in an autopsy-proved case of bilateral geniculate body necrosis. Another often cited case with bilateral lesions of the lateral geniculate bodies was reported by MacKenzie, Meighan and Pollock in 1933. Their patient had normal visual acuity in both eyes, in keeping with the apparent sparing of the macular representation in one lateral geniculate body.

Bender and Bodis-Wollner (1978) and Savino *et al.* (1978), described impaired visual acuity in at least one eye in the majority of their 33 patients with a diagnosis of an optic tract lesion. From the lists of responsible lesions given by these investigators, it appears that they were dealing primarily with suprasellar and parasellar masses: none cited a clear example of a posterior optic tract or lateral geniculate lesion. As posterior lesions apparently spare acuity as described above, the explanation for any impairment of acuity in the patients described by these investigators may have to do with anatomical peculiarities in the anterior optic tract. An involvement of both crossing and non-crossing nerve fibres from one and the same eye with a lesion restricted to the optic tract seems to require a looping of nerve fibres into the proximal tract as is sometimes described in schematic diagrams of the fibre pattern in the visual pathway. However, there seems to be no evidence for such a looping of fibres into the proximal tract in man or in monkeys (Polyak, 1957; Hoyt and Luis, 1963; Hoyt, 1970; O'Connell, 1973). Until evidence to the contrary is accumulated, it appears more rational to localize anterior visual pathway lesions with impaired acuity in one or both eyes to the optic nerve(s) or the chiasm rather than to the optic tract.

SUPRAGENICULATE LESIONS

Lesions of the suprageniculate visual pathway are of common occurrence but a precise localization of the site of injury often presents many difficulties. The organization of the posterior visual pathway is known in general outline (e.g. Spalding, 1952) but little is known about details of topography, the range of normal variability, and what displacements may occur under pathological circumstances. Irrespective of these difficulties, neither temporal lobe lesions nor parietal lobe lesions are held to influence visual acuity (Spalding, 1952; van Buren and Baldwin, 1958; Smith, 1962, and others). Surprisingly, the effects on visual acuity of the very best defined injury to the posterior visual pathway, *viz.* occipital lobectomy, are less than clear. The often cited study by Halstead, Walker and Bucy (1940) describes 2 carefully studied patients with subnormal acuity in both eyes following unilateral occipital lobectomy. Huber (1970), who studied 12 cases of the same category, found an acuity less than 1.0 in 12 of the 24 eyes. Similar observations have been made by many other investigators (*see* Dubois-Poulsen *et al.*, 1952; Huber, 1970, for reviews). However, the interpretation of results found in many previously reported cases is complicated by the presence of chronic papillœdema or other conditions capable *per se* of impairing visual acuity. The cases described by Halstead *et al.* (1940), for instance, were subjected to ventriculography *via* direct cannulation of both posterior ventricular horns. It is unrealistic to assume full integrity of the visual pathways after such procedures. Modern diagnostic tools like computed axial tomography sometimes allow a non-invasive diagnosis of an occipital lobe tumour prior to the development of pressure signs and other complications. The study of such cases should allow more precise conclusions regarding the effects on visual acuity of well defined suprageniculate lesions.

Present Investigations

The following cases are illustrative of the effects of unilateral occipital lobectomy. All had relatively discrete signs of unilateral visual pathway dysfunction prior to operation.

Case E.F. This otherwise healthy schoolgirl began suffering from periodic light phenomena in her left visual field at the age of 15 years. The attacks gradually increased in number during the following two years. Computed tomography disclosed a cystic lesion in the right occipital pole. The pre-operative neuro-ophthalmological examination revealed a visual acuity of 1.5 in both eyes, and discrete upper quadrantic depressions, homonymous to the left (fig. 7). No other abnormalities were seen. A neurological examination was normal. A right occipital lobectomy was carried out. The microscopic diagnosis was grade I astrocytoma. Following operation, she had a complete macula-splitting hemianopia, homonymous to the left. Visual acuity was 1.5 bilaterally. The visual phenomena did not recur.

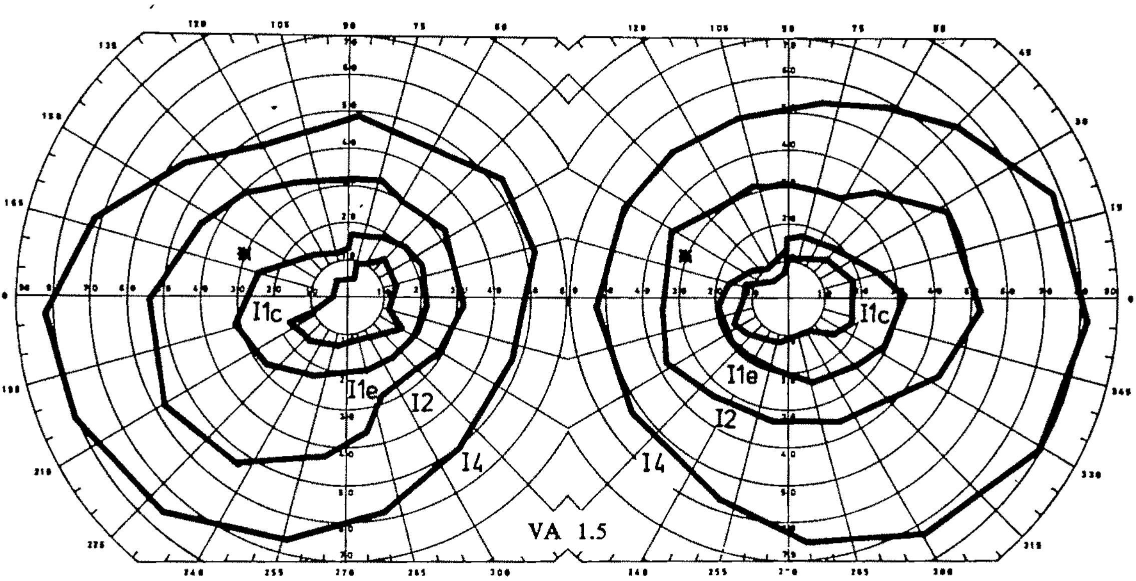

FIG. 7. *Case E.F.* Visual field defects prior to right occipital lobectomy. Note minimal signs of visual pathway disturbance. * identifies locus of recurrent light flashes (*see* text).

In this case acuity for sinusoidal gratings was also determined. Pre-operatively, the patient could resolve 46 cycles/degree ± 3 (SD) at the 50 per cent level. Post-operatively, acuity remained at 46 ± 3 cycles/degree in both eyes. Hence, there was no significant change following operation.

Case B.B. A 55-year-old male was operated on for a superficial glioblastoma multiforme on the right occipital convexity, without neurological or visual sequelæ. The operation was thought to be radical so no further treatment was given. Ten months later he noted some dimness of vision in his left visual field, and perimetry revealed a low-degree depression, homonymous to the left (fig. 8). Visual acuity was 1.0 bilaterally. There was a low-degree papillœdema in both eyes, without signs of secondary atrophy or choroidal folding. Neurological examination revealed only a slight left hemiparesis. A full occipital lobectomy was performed, resulting in a complete, macula-splitting hemianopia, homonymous to the left. Visual acuity remained at 1.0 bilaterally one week post-operatively. The presence of papillœdema was considered immaterial in this case because of its low degree, and its failure to change its appearance during the seven days separating the pre-operative and post-operative examinations.

Case R.E. A 48-year-old female was admitted for operation on a right tentorial meningioma, causing episodic headaches and flickering lights before the eyes. The pre-operative neuro-ophthalmological examination revealed an upper quadrantic

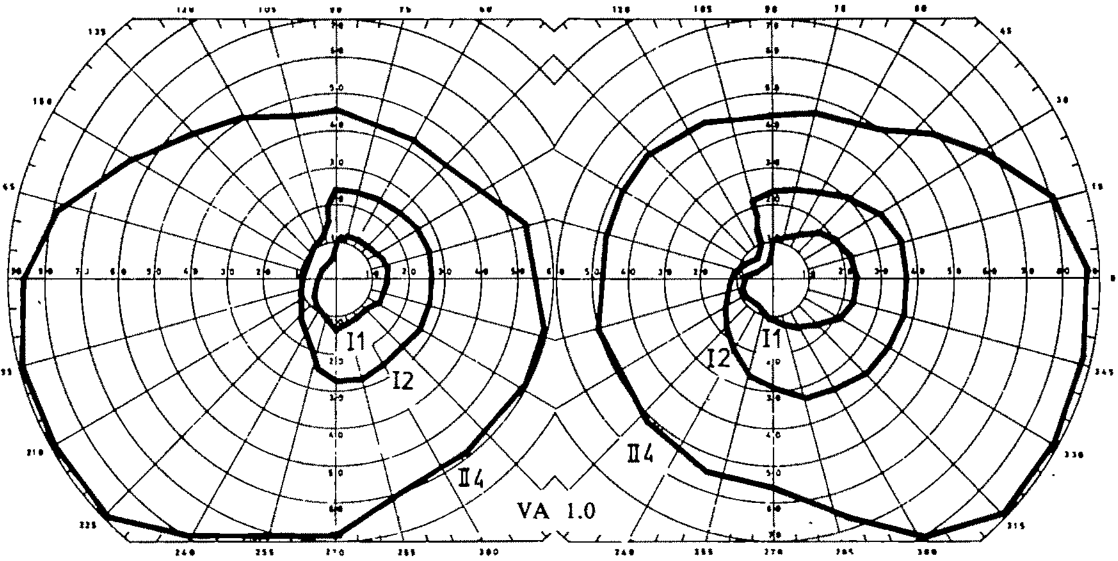

FIG. 8. *Case B.B.* Visual field defects prior to right occipital lobectomy.

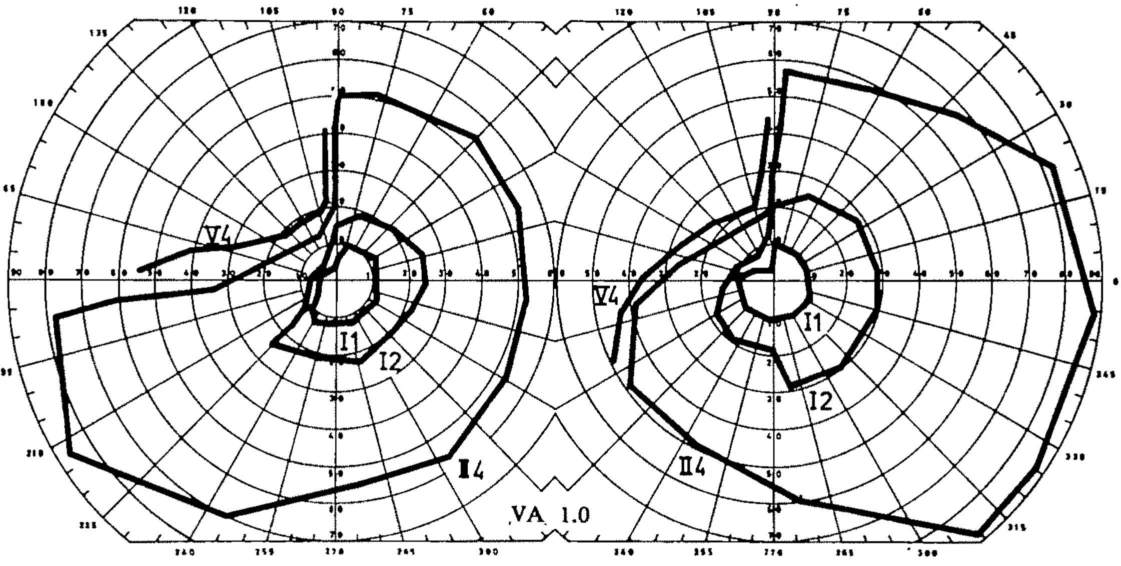

FIG. 9. *Case R.E.* Visual field defects prior to right occipital lobectomy.

field defect homonymous to the left (fig. 9) and an acuity of 1.0 bilaterally. There were no other neurological abnormalities. It became necessary to resect the right occipital lobe during operation, resulting in the production of a complete, macula-splitting hemianopia, homonymous to the left. Visual acuity remained at 1.0 bilaterally following operation.

Case E.J. A 57-year-old female was admitted with similar symptoms as Case R.E., and the same diagnosis. Pre-operatively, she had a relative field defect homonymous to the left (fig. 10), and a visual acuity of 1.0 bilaterally. There were no other neurological abnormalities. Once again, resection of the right occipital lobe was unavoidable, resulting in the production of a complete, macula-splitting hemianopia, homonymous to the left. Post-operatively, visual acuity was 1.5 in both eyes.

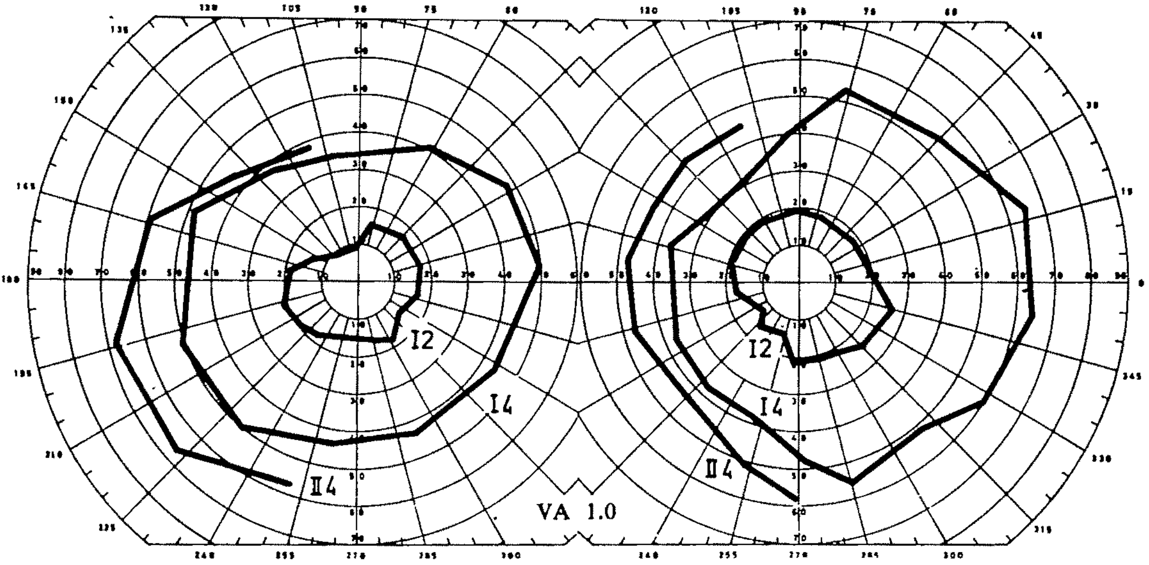

FIG. 10. *Case E.J.* Visual field defects prior to right occipital lobectomy.

Two patients with *bilateral* lesions of the occipital poles (that is, the cortical representation of the macula) merit brief description:

Case P.J. A 26-year-old male developed severe impairment of vision over a few days. On admission to the hospital, he could count fingers at 0.5 m bilaterally. Confrontation tests showed a full periphery, with retained perception of colours outside the central scotomata. The latter had a diameter of *c.* 10 degrees. Pupils, motility and fundi were normal. Computed tomography showed bilateral occipital

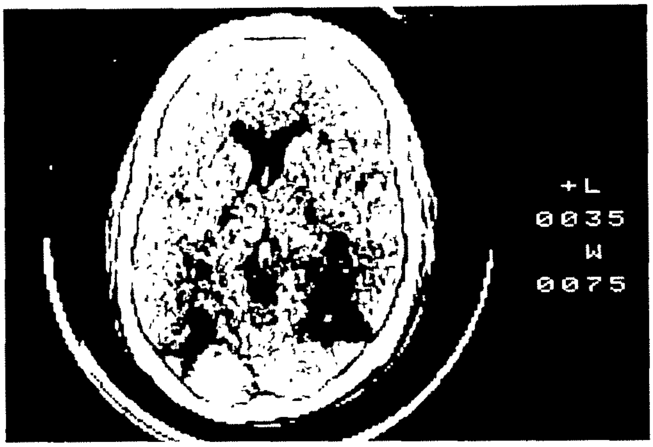

FIG. 11. *Case P.J.* Unenhanced computed axial tomography shows bilateral occipital pole metastases producing bilateral central scotomata.

pole lesions (fig. 11). Further investigations revealed widespread metastases of a non-classified, malignant tumour of the testis. The patient was not explored surgically.

Case S.O. A 65-year-old male fell 4 m from a roof and acquired an 8 × 10 cm depressed fracture of the skull centred slightly to the left of the midline, with the lower margin just above the inion. At operation, it was obvious that the depressed bone fragments had contused both occipital poles, more so on the left. Following operation, acuity was 0.6 bilaterally, and there was a field defect traversing the vertical meridian (fig. 12). There were no other neurological abnormalities.

Comment

On the basis of these observations, preservation of visual acuity can be expected following uncomplicated resection of one occipital lobe. The same lack of effect on acuity can be expected with more anterior lesions of the suprageniculate visual pathway as the primary visual cortex is the sole recipient of neurons projecting from the lateral geniculate body. Bilateral occipital pole lesions, on the other hand, can be expected to consistently impair acuity (Holmes and Lister, 1916). *Bilateral sparing* of the cortical macular representations (as may occur with bilateral occlusions of the posterior cerebral artery) usually allows retention of normal visual acuity in spite of the massive contraction of the peripheral fields (Förster, 1890; Nepple, Appen and Sackett, 1978).

None of the occipital lobectomy patients reviewed here had discernible macular sparing. Although the present observations thus fail to furnish new data on this poorly understood phenomenon (except, perhaps, increased doubt as to its existence), they tend to disprove at least one of the several hypotheses put forward for its explanation (*see* Polyak, 1957, and Walsh and Hoyt, 1969, for extensive reviews). The chessboard innervation of the retinal macula advocated by Morax (1919) and Huber (1970) appears difficult to reconcile with retention of normal visual acuity. According to the chessboard hypothesis, unilateral lobectomy should lead to a doubling of the average separation between transmitting foveal cones. This should result in a 50 per cent drop in resolution capability (Rönne, 1911; Frisén and Frisén, 1979). The finding that acuity remains unchanged is, therefore, a strong argument against the chessboard hypothesis. The recent demonstration of a chessboard-like distribution in the monkey retina of macular ganglion cells (Bunt, Minckler, and Johanson, 1977) is not contradictory: it is the distribution of foveal cones that counts. Unilateral occipital lobectomy in man obviously leaves a normal packaging density of transmitting cones in at least one half of the fovea.

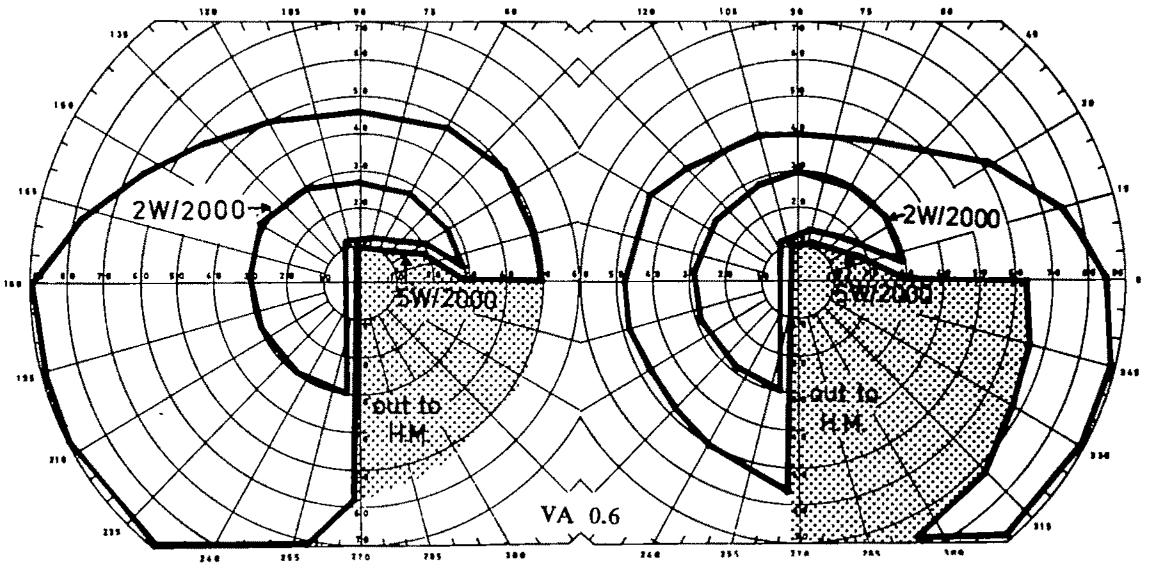

FIG. 12. *Case S.O.* Visual field defects due to bilateral occipital pole contusions. Composite diagram of tangent screen and confrontation test results. Note symmetrical impairment of visual acuity.

DISCUSSION

In the normal eye, the central region of the macula lutea, or the foveola, is the locus of maximum acuity. Acuity drops monotonically with increasing distance from this central 20′ diameter iso-acuity area, where about 2,000 cones of particularly slender dimensions are closely packed together (Polyak, 1941; Millodot, 1972). The more superficial layers of the retina, and their blood vessels, are spread sideways from this region, presumably to prevent interference with image formation (Weale, 1966). The fineness of retinal 'grain' in the foveola has long been held to be a major limiting factor for visual acuity, although its *modus operandi* has been poorly understood. Helmholtz (1867) suggested that two point sources of light can be discriminated as soon as the distance between their retinal images exceeds one cone diameter. Visual acuity, however, is not an all-or-none variable but a stochastic variable, that is, it contains random error components. Random errors arise from a multiplicity of largely independent sources. These can be exemplified as eye movements, variations in accommodation and pupil size, variations in photon incidence and absorption, and internal noise. These random errors operate to defy a sharp transition between resolvable and non-resolvable visual objects. As a matter of fact, all objects (or more precisely, all visual angles) are associated with a certain probability of discrimination. Large optotypes, for instance, may be resolved with a probability approaching 100 per cent, but with decreasing dimensions, the probability of discrimination drops according to a frequency-of-seeing curve (Lythgoe, 1932). In the normal eye, letter acuity typically drops from *c.*1.9 to *c.*1.3 as the criterion is changed from 10 to 90 per cent probability of discrimination (Frisén and Frisén, 1980). Therefore, the classical question regarding the *minimum separabile* simply cannot be answered: it needs to be rephrased within a probabilistic framework. Similarly, a theory for the neuroretinal basis of visual acuity must be expressed in probabilistic terms. Helmholtz's (1867) idea is clearly conflicting with these modern points of view. It is also in conflict with the known characteristics of retinal images (Vos, Walraven and van Meeteren, 1976). A more realistic model of the neuroretinal basis of visual acuity is that the probability of discrimination depends only on the angular separation between test pattern details, and the angular separation between foveolar cones, or simpler still, on the separation ratio. This model has been validated both in normal eyes and in eyes with abnormal cone separations (Frisén and Frisén, 1976, 1979). There are no reasons to believe that the same model should fail in eyes with disconnected cones, for example, eyes with descending optic atrophy. However, lack of data at present hinders validation for the disconnection situation.

There are many other factors capable of influencing the results of acuity testing. Adequate correction of any refractive errors is mandatory. Uncorrected visual acuity has no diagnostic interest whatsoever: testing acuity without correction is like testing the road-holding ability of an automobile without tyres. Other important factors include the nature of the test, the spatial separation between test symbols, and the illumination level. Different letter tests may give quite diverging results because of dissimilar legibility of various test letters, unequal scale factors, and poor standardization (Sloan, 1951; Vos, 1971). Most important from a procedural point of view is a reasonable definition of results. Many investigators require that all letters on one and the same line are correctly identified to merit credit. Such a criterion will nearly always lead to a falsely low estimate of visual acuity: it is usually possible for a given subject to read several letters on the following line, and a few letters also on the next one. A 50 per cent correction identification criterion has many advantages from a statistical point of view (Frisén and Frisén, 1979).

Accurate assessment of optotype visual acuity requires access to a visual acuity chart with letters of equal legibility, with appropriate spacing of letters and letter sizes and several levels corresponding to acuities above 1.0. As mentioned in the Introduction, and further supported by the findings in this study, an acuity level below 1.0 should never be accepted as normal. The actual level of normal optotype acuity is poorly known. Several studies have been made of visual acuity, e.g. as a function of age, but these studies have rarely included optotypes corresponding to acuity levels above 1.0 (*see* Slataper, 1950).

Also the present study fails to meet all modern demands for a well controlled acuity test. This is due to the use of a standard acuity chart, based on letters of unequal legibility, and an insufficient number of test lines above 1.0. These faults were partially compensated by the use of constant test conditions, pre- and post-operative observations and a relatively large number of cases, and, in some cases, the complementary use of finely graduated sinusoidal gratings. On these grounds, the present results can be held to be valid.

Lately, much interest has been focused on more extensive tests of central vision, *viz.* determinations of spatial contrast sensitivity. These tests aim to determine what level of contrast is required to allow recognition of test patterns. Typically, sinusoidal gratings of variable spatial frequency and contrast are used. In the normal eye, peak sensitivity occurs at about 5 cycles/degree (approximately equivalent to 0.15 or 20/120 optotypes), and falls monotonically for both higher and lower frequencies. The normal contrast sensitivity curve is therefore roughly similar to an inverted U, where the right-hand foot-point is a measure of visual acuity (i.e., the highest spatial frequency detectable at maximum contrast). Several studies have been made of spatial contrast sensitivity in patients with various neurological diseases (Bodis-Wollner and Diamond, 1976; Regan, Silver and Murray, 1977; Arden and Gucukoglu, 1978). These studies have shown that spatial contrast sensitivity frequently becomes abnormal in neurological disease. Abnormal contrast sensitivity curves have often been obtained in patients whose visual acuity remains ‘normal or nearly normal’ but this is insufficient ground for comparison. The vastly different natures of the two tests make a meaningful comparison difficult. However, nonspecific factors like fatigue might be expected to influence the subject’s criterion setting to a larger degree in the unaccustomed test situation associated with contrast sensitivity measurements. These latter tests may therefore be more prone to produce nonspecific impairments of results. However, experiences gained with parallel measurements of letter acuity and spatial contrast sensitivity in this laboratory (Frisén and Sjöstrand, 1978; J. Sjöstrand, in preparation) indicate that the results of the two tests tend to be very closely related.

The capacity for visual resolution is not an exclusive foveal function: visual acuity can be measured anywhere in the visual field (Wertheim, 1894; Frisén and Glansholm, 1975). Peripheral visual acuity is known to fail in many types of disorders of the visual pathways (Heron, Milner and Regan, 1975). Knowledge of what retinal area a given subject uses when testing visual acuity may be open to discussion, at least when acuity is subnormal (Williams and Gassel, 1962). However, there are reasons to assume that previously normally sighted individuals retain their fixation reflexes: a patient with a severe macular degeneration, for instance, has to learn actively to turn an intact paracentral retinal area towards objects to be scrutinized. The commonplace observations that active learning seems to be required to move fixation out of the foveola suggests that acuity tests ordinarily assess foveolar function (Aulhorn, 1973). This is not true for tests of spatial contrast sensitivity: these tests typically utilize stimulus displays of a very much larger subtense than the iso-acuity area of the fovea. The results of these latter tests may also to some extent be influenced by extrageniculostriate visual mechanisms, which appear to have too low resolution capabilities to influence ordinary visual acuity tests (Weiskrantz, Warrington, Sanders and Marshall, 1974).

On the basis of the present results, it may be argued that properly executed visual acuity tests are powerful tools for the detection of optic nerve and chiasmal disorders. However, they have no value in the detection of unilateral lesions of the retrochiasmal visual pathway: acuity remains normal in patients with unilateral lesions of the optic tract, the lateral geniculate, and the suprageniculate visual pathway. Bilateral lesions of the retrochiasmatic visual pathway may produce impaired acuity: acuity will then be symmetrically affected in both eyes. Asymmetric impairment of visual acuity points to optic nerve and/or chiasmal lesions. An acuity level below 1.0 always demands an explanation.

SUMMARY

A series of patients with well defined lesions of various parts of the visual pathways was studied in an attempt to illuminate the neuropathophysiology of visual acuity. Acuity was found to remain normal in all cases with unilateral retrochiasmal lesions, including those of the optic tract. Bilateral retrochiasmal lesions involving the foveal nerve fibres on both sides impaired acuity to the same degree in both eyes. Lateral chiasmal lesions regularly produced impaired acuity in the ipsilateral eye. Midchiasmal lesions commonly led to an impairment of visual acuity in both eyes, usually asymmetrically, and roughly proportionate to the severity of the visual field defect. Compression optic neuropathy was found to reduce acuity in rough proportion to the severity of compression. It was concluded that acuity remains normal as long as either the crossing or the non-crossing neural outflow from the retinal fovea remains intact: acuity fails only

when both sets of nerve fibres are compromised. A properly executed acuity test seems to be a powerful tool for detecting such conditions. The lower limit of normal acuity should never be set below 1.0 or 20/20: even this level is clearly subnormal in many subjects.

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CLINICAL AND MORPHOLOGICAL FEATURES OF GOLD NEUROPATHY

by S. M. KATRAK, M. POLLOCK, C. P. O'BRIEN, H. NUKADA,
S. ALLPRESS, C. CALDER, D. G. PALMER, D. M. GRENNAN,
P. L. McCORMACK *and* M. R. LAURENT

(*From the Divisions of Neurology and Rheumatology, Department of Medicine,
University of Otago Medical School, Dunedin, New Zealand*)

INTRODUCTION

GOLD salts have been used in the treatment of rheumatoid arthritis for over fifty years. While toxic reactions involving skin, blood and kidneys are frequent, neurological complications are regarded as uncommon. There are, for example, few reports of gold-induced peripheral neuropathy (Lescher, 1936; Leiper, 1946; Doyle and Cannon, 1950; Endtz, 1958; Walsh, 1970) and only one with a morphological description (Walsh, 1970).

In this study we report clinical, neurophysiological and quantitative light and ultrastructural features of three patients who developed gold-induced peripheral neuropathy. Two patients were of particular interest because they manifested myokymia. In the light of the clinical and morphological findings we undertook an additional investigation of peripheral nerves in hens pre-treated with sodium aurothiomalate (Myocrisin, M and B).

CASE REPORTS

Case 1

C.T. (A269353) Born 1928, clerk. This patient has had rheumatoid arthritis since 1971. When seen in November 1976 he had generalized active rheumatoid disease without clinical evidence of Sjögren's syndrome. His hæmoglobin was 13.9 g/dl, WBC 11 200/μl and ESR 18 mm at one hour. Rheumatoid factor was positive at 1 in 64 (Rose Waaler). A course of intramuscular gold (Myocrisin, 50 mg weekly) was commenced after incremental test doses.

In mid-January 1977, having received 490 mg of gold, he complained of a sore mouth and generalized itching. A blood screen revealed a mild eosinophilia. No further gold was given but nine days later he complained of a more severe burning sensation in his mouth and of a blotchy erythematous rash in his legs. He began to experience pins and needles in both feet, worse on the left, and painful cramps in his calves and thighs. He had also noted rippling of the muscles in his feet with spontaneous movements of his toes. While his rash, sore mouth and numbness improved over the next three days, muscle rippling spread to involve his calves and thighs and intermittently his whole body. On neurological examination the principal abnormalities were confined to his legs. He had continuous undulating movements in the calves, thighs and feet which differed from fasciculations in that they were coarser and the contraction rippled along the same course repeatedly. There was neither voluntary nor percussion myotonia. Weakness predominated in tibialis anterior, peroneal and the intrinsic muscles of the feet, with mild foot drop on the left. The knee jerks were brisk but the right ankle jerk absent and the left sluggish. While his feet felt cold, they were warm to the touch. Perception of pain, hot and cold were impaired from just below the knees. Pin-prick was also impaired in the fingers and thumb of the right hand and two-point discrimination abnormal in the right little finger. Touch, vibration and position sense were preserved. The peripheral nerves were not thickened.

Investigations. Full blood count, urea and electrolytes, urinary porphyrin and serum IgG, IgM, IgE, C3 and C4 were normal. Serum IgA was slightly reduced at 0.7 g/l (normal 1-3). A glucose tolerance curve was normal, as was the CSF examination. Serum gold levels varied between 3.0 μmol/l and 3.6 μmol/l while the CSF gold level was 1.2 μmol/l.

One week after starting treatment with phenytoin sodium 100 mg t.i.d. and carbamazepine 200 mg b.d. he obtained relief from both cramps and myokymia. Both drugs were discontinued on May 30, 1977 without return of symptoms. By June 1977 only minimal weakness of the left peroneii remained and both ankle jerks were brisk. Apart from slow but correct responses to hot and cold testing below the knees there was no sensory impairment.

A sural nerve biopsy was performed in March 1977.

Summary. A 49-year-old man with rheumatoid arthritis developed polyneuropathy and generalized myokymia in association with stomatitis and dermatitis after receiving 490 mg of intramuscular gold. His myokymia responded dramatically to drug therapy and after five months his neurological recovery was almost complete.

Case 2

V.M. (B065022) Born 1907, housewife. The patient in 1963, when aged 56, insidiously developed pain and swelling in her shoulders, right knee and left ankle. Over the next eight years she had progressive involvement by rheumatoid disease of hands, feet, knees, shoulders and cervical spine. She was treated intermittently with non-steroidal and anti-inflammatory drugs and between 1970 and 1971 received 3 mg of prednisone *nocte*. Her hæmoglobin was 11.1 g/dl, WBC 6,800 μl, ESR 65 mm at one hour. The rheumatoid factor was positive at a titre of 1/128. A course of gold injections (50 mg weekly of myocrisin) was started in January 1972. When seen in July 1972 she first complained of a gritty sensation in her fingertips. She had noted no other symptoms suggestive of gold toxicity and regular urine testing for proteinuria and peripheral blood tests for platelet and differential white cell counts were unremarkable. Gold therapy was continued in fortnightly injections. The feeling of sand on her skin spread slowly to the mid-palmar region. Concurrently she began noting she had 'to take a run' to ascend high steps and that her hands were weak. During the following two months a numbness began in the soles, and gradually ascended to the knees. The weakness in her arms and legs steadily worsened. In November 1972, having received a total of 1310 mg of gold, Myocrisin was discontinued and she was admitted to hospital.

On examination there was evidence of a severe polyneuropathy. Atrophy and weakness were most marked distally in the limbs, associated with fasciculations in the hands. Power was reduced to MRC grade 1 (Medical Research Council, 1943) in the intrinsic hand muscles and to grade 2 in the shoulders. There was also a reduction in power in the hips to grade 3 on the right and to grade 2 on the left. The patient could dorsiflex the feet through an arc of only 15 degrees and the toes through only 5 degrees. Tone was reduced in the legs and arms. The peripheral nerves were not thickened and the muscles non-tender. Stretch reflexes were reduced (biceps and supinator) or absent (triceps, knee and ankle) and the plantar responses flexor. Light touch, pain and temperature sensation were impaired but not lost in a glove and stocking distribution shading off to normal at the knees and in the mid-forearms. Position sense was lost in the toes and vibration sense absent below the hips. There was no abnormality of mentation and the cranial nerves were intact. Articular examination revealed the presence of a synovitis in the elbows, ankles, hands and shoulders but her arthropathy was less active than before the institution of gold therapy. There were no skin rashes and no evidence of a cutaneous vasculitis.

Investigations. A full blood count, plasma proteins, fasting blood sugar, urinary porphyrin, serum vitamin B12, urea and electrolytes were normal. Both the Rose Waaler test and VDRL were negative. The creatinine clearance was 115 ml/min with 0.1 g of protein excreted per 24 h. A rectal biopsy was negative for amyloid.

Following admission a ten-day course of dimercaprol was given. While serum gold fell over four days from 10.3 μmol/l to 4.6 μmol/l motor function continued to deteriorate and one month after admission as a result of severe proximal limb weakness she became unable to walk. A fourteen-day course of penicillamine, 600 mg daily, was begun. Four weeks later neurological abnormalities began to improve and she recommenced walking in a frame. By April she had regained 20 degrees of dorsiflexion in both feet and sensation had returned to normal. She progressed to walking with the aid of gutter crutches and late in April was discharged. The patient has since been able to walk without the use of aids, but has been left with bilateral foot drop and absent ankle jerks.

A sural nerve biopsy was performed in December 1972.

Summary. A 65-year-old patient with rheumatoid arthritis developed a severe sensorimotor polyneuropathy after receiving 1310 mg of intramuscular gold. A slow recovery of neurological abnormalities was incomplete and the patient was left with bilateral foot drop.

Case 3

H.T. (R247980) Born 1931, waterside worker. This patient developed pain and swelling in his left shoulder in 1971. Joint pains continued and in July 1974 he was noted to have soft tissue swelling of interphalangeal and metacarpophalangeal joints and bilateral knee effusions. Tenderness and limitation of movement were noted in his wrists, left elbow and both shoulders. His hæmoglobin was 13.2 g/dl, ESR 77 mm at one hour and rheumatoid factor positive at a titre of 1 in 32.

A course of intramuscular gold (Myocrisin, 50 mg weekly) was commenced in August and over the next four months the patient's articular symptoms improved. However, in December 1974 he developed numbness in the tips of his fingers and toes. Paræsthesiæ resolved in the fingers over two weeks but persisted in the toes. Weekly gold injections were continued until March 1975, when the patient first noted weakness in the feet and numbness extending to the ankles. Weakness progressed rapidly and over the following week he became unable to drive, to walk, and finally to stand.

Examination showed that his marked bilateral limb weakness was most marked distally in the legs. Power was reduced to MRC grade 4 proximally in the arms, to grade 3 in the hands, to grade 4 in the hips and to grade 2 at the ankles. Persistent myokymia was present in the left calf and foot. The limbs were hypotonic and areflexic. Light touch, pain, and temperature were impaired distally in the hands and feet and although position sense was slightly reduced in the toes, vibration sense was intact. Peripheral nerves were neither enlarged nor tender. Articular examination showed no evidence of rheumatoid disease or of vasculitis.

Investigations. His hæmoglobin was 12.1 g/dl, WBC 9700/μl, with a normal differential and ESR 55 mm at one hour. The rheumatoid factor was positive at 1 in 64. Blood urea, electrolytes, serum proteins and urinary prophyrin were normal. A glucose tolerance test was normal as was an ECG and chest x-ray. Apart from a protein of 588 mg/dl, the CSF was normal. The CSF gold and protein levels monitored over a ten-month period are seen in Table 1.

TABLE 1. GOLD AND PROTEIN MEASUREMENTS IN CASE 3 DURING 1975

	March	*April*	*May*	*July*	*November*	*December*
Serum gold (μmol/l)	11.0	5.6	6.3	—	—	—
CSF gold (μmol/l)	2.7	—	1.2	1.1	0.5	0.66
CSF protein (mg/dl)	588	397	165	257	139	99

During March the patient was treated with a two-week course of dimercaprol. A gradual improvement of sensory loss and limb weakness occurred over the next three months with a return of all stretch reflexes. However, his motor recovery was incomplete and eighteen months later he still had bilateral foot drop and distal weakness in the arms sufficient to prevent him from returning to work. Myokymia was still present in the left leg.

A sural nerve biopsy was performed in April 1975.

Summary. A 44-year-old male patient developed paræsthesiæ followed by a severe sensorimotor polyneuropathy after receiving 1350 mg of Myocrisin. Slow neurological improvement occurred but he has been left with residual weakness.

METHODS

Fascicular sural nerve biopsies were taken from the three rheumatoid patients, 2 to 5 cm above the lateral malleolus under local anæsthesia. Human control nerve had been previously obtained from unpaid volunteers who had given informed consent (Declaration of Helsinki) selected on the basis of a normal neurological evaluation and normal nerve conduction studies.

For animal studies adult white leghorn hens, weighing 1.2 to 2.1 kg, were obtained from a local battery. They were housed singly in battery cages and fed chick feed and water freely. Sodium aurothiomalate (Myocrisin) was given in weekly intraperitoneal injections. After weighing, the hens were assigned to 1 of 3 groups such that:

(1) 10 hens received 10 mg/kg body weight of gold salt weekly for 2 to 41 weeks (low dose);
(2) 5 hens received 20 mg/kg body weight of gold salt weekly for 16 weeks (high dose);
(3) 7 hens formed a control group.

All animals had weekly blood counts and urea estimations.

Sensory nerves in the hen were taken for morphological study from the cutaneous branch of the superficial peroneal nerve immediately proximal to the ankle and from a distal extension of this nerve to the third toe. A proximal sample of hen mixed motor nerve was taken from the lateral ischiadic nerve. Distal mixed motor nerve was taken from the branch of the deep peroneal nerve innervating extensor hallucis brevis.

Both hen and human nerve were processed in the following way: specimens were fixed initially in 2 per cent glutaraldehyde in 0.1 M cacodylate buffer (pH 7.40) at room temperature, followed by 1 per cent osmium tetroxide in the same buffer. The portion of nerve for teasing in glycerol was fixed in glutaraldehyde for 10 to 15 min and in osmium tetroxide for 1½ h. Portions to be embedded in epoxy were fixed for 1½ to 2 h in glutaraldehyde and for 1½ h in osmium tetroxide.

Single teased fibres, each with a minimum of four internodes were obtained from each nerve using fine watchmaker forceps. Fibres were teased in approximately equal numbers and without preselection from each of the available fascicles. Single nerve fibres were graded descriptively as: (A) normal appearance; (B) marked irregularity of myelin; (C) segmental demyelination; (D) segmental demyelination and remyelination as evidenced by at least a 50 per cent reduction in myelin thickness; (E) linear rows of myelin ovoids; (F) segmental remyelination with internodes showing 50 per cent or more difference in myelin thickness; (G) focal irregularity of myelin forming globules or 'sausages'; and (H) myelin ovoids contiguous to two or more thinly myelinated internodes.

Photographic enlargements of transverse epoxy sections were used to estimate the number and diameter histogram of myelinated fibres/mm^2 of transverse fascicular area. The Zeiss particle size analyser Model TGZ3 was used to express the results as an exponential frequency distribution curve. The exact magnification was obtained from photographs of a reticle. Fibres not measured because of artifact were used in the calculation of total number of fibres/mm^2.

The following additional morphological studies were undertaken only in patient and control nerves.

Evidence of a vasculitis was sought on frozen sections of sural nerve stained with hæmatoxylin and eosin, or Gomori trichrome.

Internode lengths of teased nerve fibre were measured using an ocular micrometer. For each teased fibre the mean internode length and the coefficient of variation of internode length were calculated. For statistical analysis a 'small fibre' was defined as having a mean internode length of less than 625 μm and a 'large fibre' as having a mean internode length of 625 μm or more.

Thin sections of control and patient's sural nerves were compared in a Philips 300 electron microscope. Measurements were made on electron micrographs of 100 myelinated fibres as encountered serially in X and Y traverses. Care was taken to obtain true transverse sections, and magnifications were checked against a diffraction grating at each viewing session. The area of each axis cylinder was then determined in μm^2 using programmed digitization and calculation. Major dense lines, and hence the number of myelin lamellæ, of each myelinated fibre were also counted through a dissecting microscope. The regression analysis of logarithm (to base e) of area of axis cylinder on number of myelin lamellæ was then determined.

Unmyelinated fibre counts were undertaken by examining a series of adjacent, non-overlapping electron micrographs printed at final magnification of 10,800. In each nerve unmyelinated fibres in 35 photographs (area = 0.013 mm^2) were counted and measured with a Zeiss TGZ3 particle analyser set on a linear scale. All axons enclosed by Schwann cells with a mesaxon and without myelin were counted as unmyelinated fibres. On the same photographic enlargements, numbers of Schwann cells, fibroblasts, macrophage nuclei, collagen pockets and clusters of denervated Schwann cells were determined per mm^2 of fascicular area.

Electromyography in patients was performed with conventional concentric needle electrodes, using a Medelec electromyographic apparatus. Nerve conduction studies were performed with surface stimulating and recording electrodes. Sensory nerve conduction was studied antidromically.

Motor nerve conduction studies were carried out in hens under pentobarbitone anæsthesia (0.4 ml/kg). In all animals velocity measurements were made before killing and in some animals prior to gold treatment. Recordings of muscle action potentials were made from needle electrodes inserted into the crural interossei. The ischiadic nerve was directly stimulated just distal to the pelvis and the superficial tibialis plantaris nerve directly stimulated just proximal to the ankle. The latencies of the onset and first peak of each potential were measured, and the amplitude taken as the peak to peak voltage. The distance between the two stimulus points was taken as a direct line with the leg straight. Hen temperatures were recorded during such studies from a thermometer inserted into the cloaca.

Human lymphocyte transformation studies were undertaken immediately following the onset of the neuropathy in Case 3 and eighteen months and four years, respectively, after the onset of neuropathy in Cases 1 and 2. Peripheral lymphocytes were separated from heparinized blood on Ficall-sodium diatrizoate gradients by a modified Böyum technique (1968). The washed separated cells were resuspended at a density of 1 × 10^6/ml in Dulbecco's minimal essential medium. Lymphocytes were cultured in the presence or absence of sodium aurothiomalate for six days at 37° C. *In vitro* concentrations of gold varied from 5 μm to 1 mM. One μCi of tritiated thymidine (21 Ci/mmol) was added twenty hours prior to harvesting. The filters were dried and the radio-activity measured by liquid scintillation counting.

RESULTS

Human Peripheral Nerve Morphology

The grading of teased myelinated fibres of sural nerves from gold-treated patients and control subjects (Table 2) revealed a statistically significant difference in the incidence of abnormalities ($P < 0.01$). Two patients (Cases 1 and 2) had a pathological incidence of axonal degeneration (condition E) (fig. 1A) and the third a striking increase in internodes with at least a 50 per cent reduction in myelin thickness (condition F) (fig. 1B).

TABLE 2. GRADING OF TEASED MYELINATED FIBRES IN SURAL NERVES OF PATIENTS WITH GOLD NEUROPATHY AND CONTROLS

Subject	*Distribution of types of fibres* (%)[1]							*Abnormal*[2]
No.	*A*	*B*	*C*	*D*	*E*	*F*	*G*	(%)
Case 1	84	0	0	0	7	8	1	16
2	77	0	2	0	7	14	0	23
3	50	0	1	0	2	47	0	50
Control								
4	98	0	1	0	0	1	0	2
5	91	0	0	0	1	8	0	9
6	94	0	0	0	0	6	0	6
7	89	0	0	1	1	9	0	11
8	92	0	1	1	0	6	0	8
9	91	0	0	0	0	9	0	9

[1] *See text* for explanation of fibre types. [2] Mean percentage of abnormal patient fibres = 29.67 ± 17.95. Mean percentage of abnormal control fibres = 7.5 ± 3.15.

While the mean internode lengths of small and large nerve fibres from gold-treated patients did not differ significantly from controls (Table 3) the mean of the coefficients of variation of internode lengths for large nerve fibres from gold-treated patients was increased.

A normal bimodal distribution of diameters of myelinated fibres was seen in two gold-treated patients but a reduction in population of large myelinated fibres present in Case 2 (fig. 2). However, there was no statistically significant difference in mean myelinated fibre densities between patients and controls (Table 4). Frozen sections revealed no evidence of vasculitis.

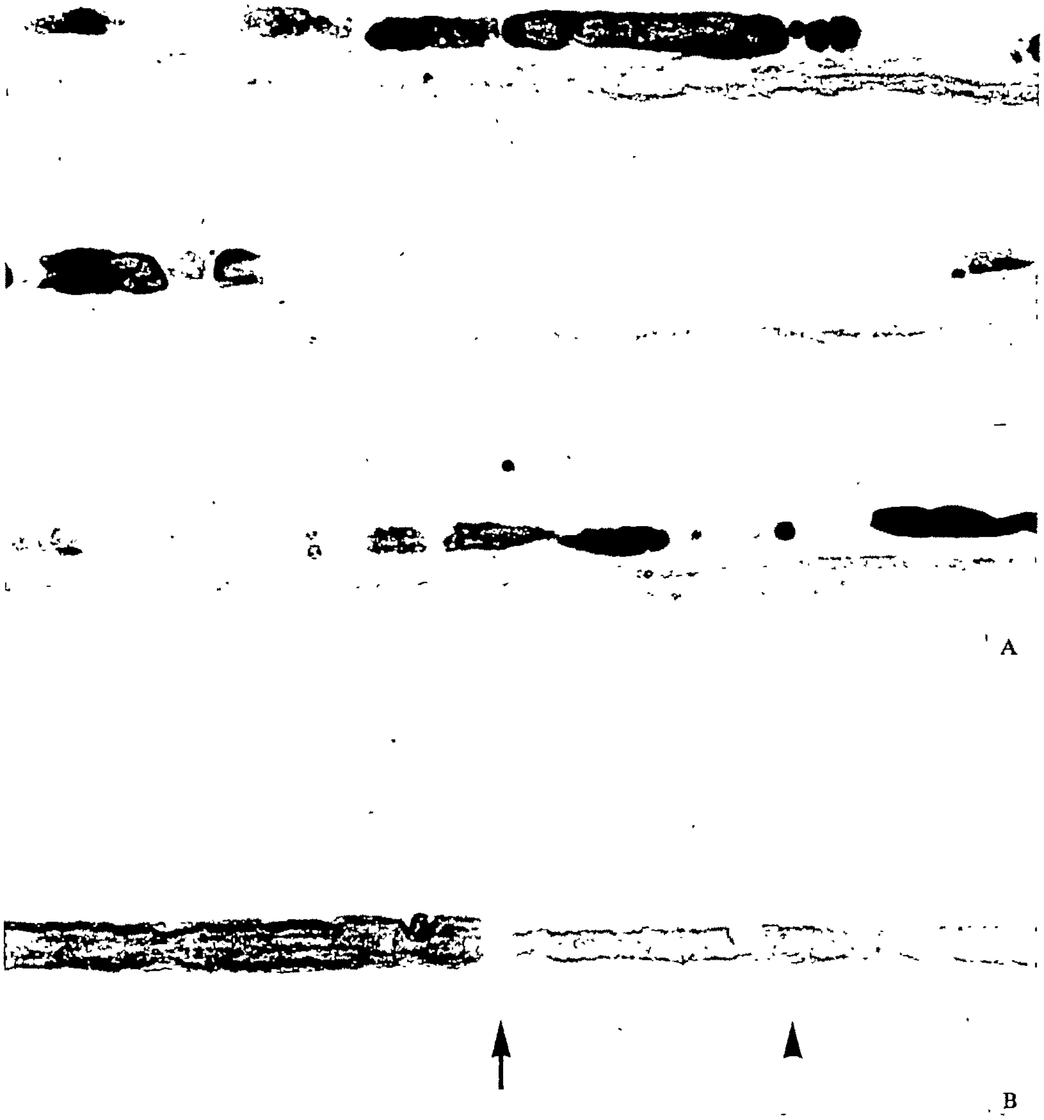

FIG. 1A, *Case 1.* Consecutive strips along teased nerve fibre from patient with gold neuropathy showing axonal degeneration (type E change). B, *Case 3.* Teased fibre from patient with gold neuropathy showing remyelinated (type F) internode (arrow-head) and node of Ranvier (arrow).

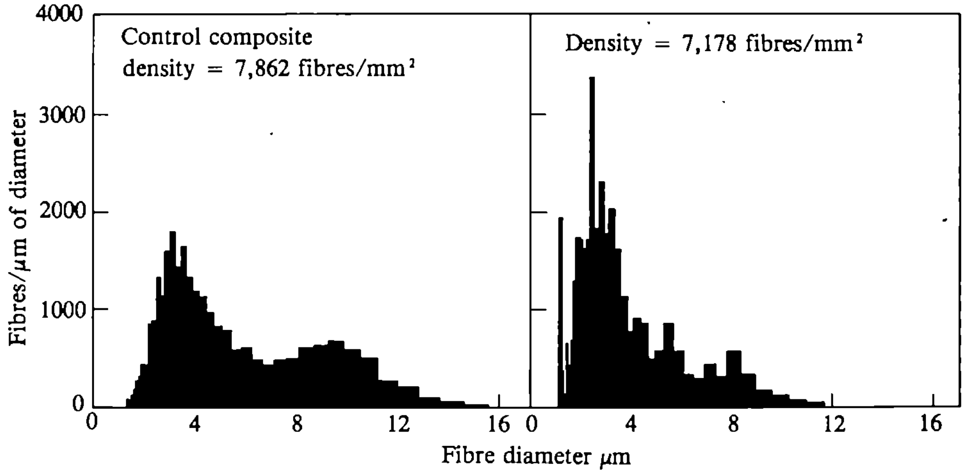

FIG. 2. Distribution of diameters of myelinated fibres in sural nerves of control (*left*) and Case 2 (*right*).

TABLE 3. INTERNODE LENGTHS OF SURAL NERVES IN PATIENTS WITH GOLD NEUROPATHY AND CONTROLS

	Small fibres[1]		*Large fibres*[2]	
Subject(s)	*Mean IL*[3] (μm)	*Mean CV*[4] (%)	*Mean IL* (μm)	*Mean CV* (%)
Case 1	122	14.9	857	10.4
2	355	17.8	782	25.3
3	450	20.5	1015	14.2
Case mean	309	17.7	885	16.6
SD	169	2.8	118	7.7
Control mean	364	18.7	864	12.6
SD	44	2.5	114	1.6

[1] Mean IL < 625 μm. [2] Mean IL $\geqslant 625$ μm. [3] Internode length. [4] Coefficient of variation.

TABLE 4. DENSITY OF MYELINATED FIBRES IN SURAL NERVES OF PATIENTS WITH GOLD NEUROPATHY AND CONTROLS

Subject(s)	*Age*	*Sex*	*No./mm^2*	*Mean*	*SD*
Case 1	49	M	8686		
Case 2	65	F	7178		
Case 3	44	M	10576		
Patient				8813	1703
Control (n = 12)				8242	2214

While a qualitative analysis of electron micrographs was undertaken in all three patients' nerve biopsies, fixation was considered satisfactory for quantitative studies only in Cases 1 and 3. Myelinated fibres showed evidence of axonal degeneration with a significant increase ($P < 0.05$) in macrophage nuclei (Table 5). Frequent Schwann cells contained myelin debris (figs. 3A and B), lipid (fig. 4A) or occasionally a large unmyelinated axon (fig. 4B). However, a comparison of regression coefficients (to base e) of area of axis cylinder on number of myelinated lamellæ (fig. 5) indicated no significant difference between biopsies from patient and controls. Further quantitative electron microscopy revealed no statistically significant difference in the densities of unmyelinated nerve fibres, denervated Schwann cells, fibroblast and Schwann cell nuclei or collagen pockets (Table 5).

TABLE 5. QUANTITATIVE VALUES OF SURAL NERVES IN PATIENTS WITH GOLD NEUROPATHY AND CONTROLS (PER mm^2)

		Nuclei				
Subject(s)	*Unmyelinated fibres*	*Schwann*	*Fibroblast*	*Macrophage*	*Collagen pockets*	*Denervated Schwann cells*
Case 1	29444	3730	397	79	4603	79
Case 3	28794	2695	638	71	6525	71
Controls[1]	24874	2530	318	21	5706	247
SD	3919	703	153	33	2314	239

[1] Mean No. per mm^2 in 7 control nerves.

Animal Morphology

The staining of hen myelin with osmium was not always uniform. Unfortunately 2 per cent potassium permanganate, while providing excellent electron contrast of hen myelin lamellæ, resulted in nerve fibres which were too brittle to tease adequately (Wight, 1969).

Teased fibre analysis of the lateral ischiadic nerve in all 5 hens given 20 mg/kg of gold weekly for sixteen weeks showed pathological changes (Table 6). In 2 hens (1 and 2) over 50 per cent of teased fibres exhibited axonal degeneration. The remaining hens in this group had a greater than 50 per cent incidence of segmental demyelination. Mean numbers of myelinated fibres/mm^2 of transverse fascicular area for this group were significantly reduced ($P < 0.01$) compared with controls (Table 7, figs. 6A and B).

Teased fibre analysis of proximal and distal motor and sensory nerves in 7 hens given 10 mg/kg of gold weekly showed less abnormal teased nerve fibres ($P < 0.005$) (Table 8). In Hens 10, 11 and 13 the predominant change in peripheral nerves was of axonal degeneration (condition E) but in Hen 14 there was prominent demyelination (condition C). It was of interest that axonal degeneration was most marked proximally in Hen 11 and distally in Hen 10.

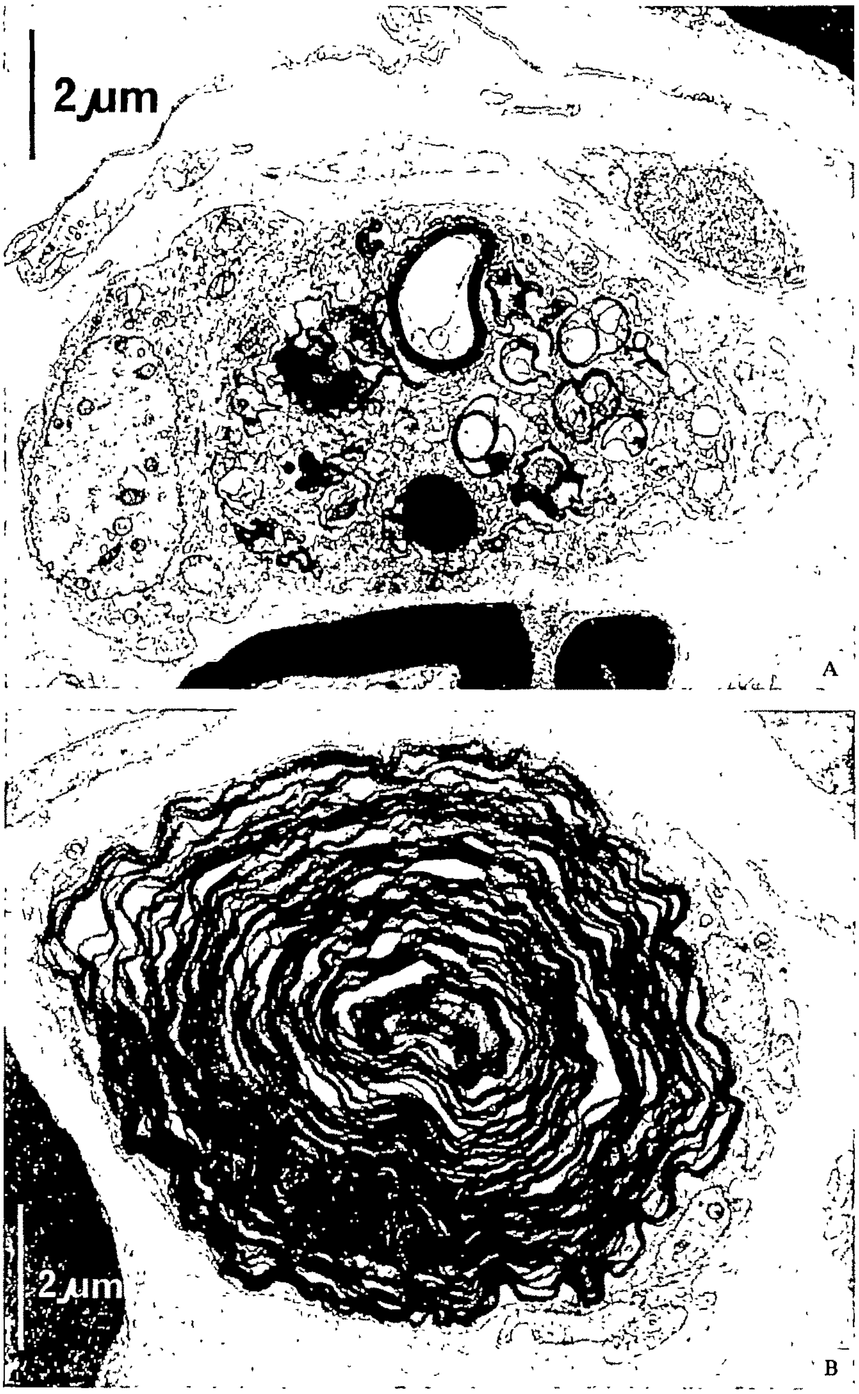

FIG. 3A, electron micrograph of transverse section through sural nerve from Case 3 showing axonal degeneration (type E change). B, electron micrograph of a transverse section through sural nerve from Case 2 showing a Schwann cell containing a prominent laminated myelin body.

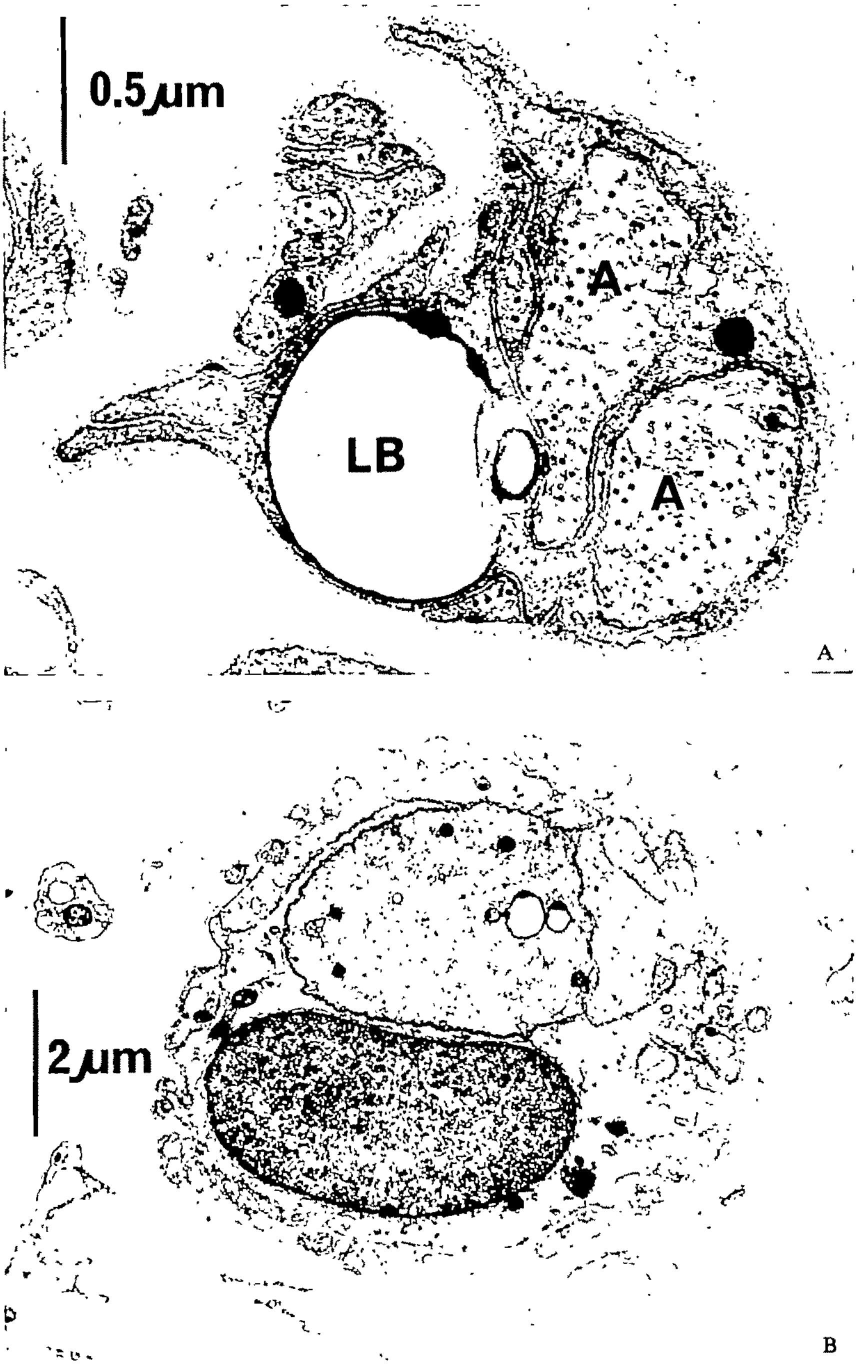

FIG. 4A, electron micrograph of transverse section through sural nerve from Case 3 showing a Remak cell with two unmyelinated axon profiles (A) and prominent lipid bodies (LB). B, electron micrograph of a transverse section through the sural nerve from Case 3 showing a Schwann cell containing a large (mean diameter 3.7 µm, area 11 μm^2) non-myelinated axon.

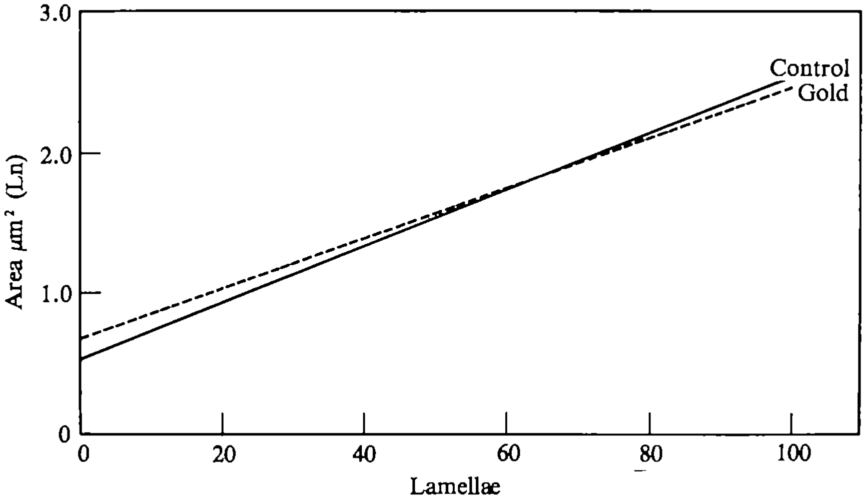

FIG. 5. Mean regression lines for area of axis cylinder (log to base e) and number of myelin lamellæ in sural nerve biopsies for patients with gold neuropathy (broken line) and controls (solid line).

TABLE 6. GRADING OF TEASED MYELINATED FIBRES IN HEN ISCHIADIC NERVE

	Distribution of types of fibres				
Hen No.	*A*	*C*	*E*	*F*	*Abnormal* (%)
Gold-treated[1]					
1	14	5	48		79
2	13	10	39		79
3	24	34		2	60
4	25	33	3		59
5	20	39			66
Controls					
6	51			1	1.9
7	51		2		3.8

[1] 20 mg/kg of gold weekly for 16 weeks.

TABLE 7. DENSITY OF MYELINATED FIBRES IN HEN ISCHIADIC NERVE

	No./mm²	*SD*
Gold group	17009	1500
Control group	28664	2153

TABLE 8. GRADING OF TEASED MYELINATED FIBRES IN PERIPHERAL NERVES OF GOLD-TREATED HENS[1] AND CONTROLS

Hen No.	*Nerve*	*Distribution of types of fibres (%)* *A*	*C*	*D*	*E*	*F*	*Abnormal (%)*
Gold-treated							
8	PM[2]	98	2	0	0	0	2
	PS[3]	98	2	0	0	0	2
	DM[4]	93	2	0	5	0	7
	DS[5]	92	6	0	0	2	8
9	PM	94	2	0	0	4	6
	PS	94	2	0	0	4	6
	DM	94	2	0	2	2	6
	DS	98	0	0	2	0	2
10	PM	82	12	0	2	4	18
	PS	67	10	0	23	0	33
	DM	51	0	0	49	0	49
	DS	78	7	0	15	0	22
11	PM	40	2	0	54	4	60
	PS	—	—	—	—	—	—
	DM	88	4	0	6	2	12
	DS	86	6	0	8	0	14
12	PM	88	8	0	0	4	12
	PS	92	8	0	0	0	8
	DM	86	6	2	0	6	14
	DS	94	4	0	0	2	6
13	PM	86	8	0	6	0	14
	PS	90	6	0	0	4	10
	DM	91	0	0	9	0	9
	DS	75	8	2	2	13	25
14	PM	78	18	0	0	4	22
	PS	46	46	2	0	6	54
	DM	80	6	0	4	10	20
	DS	48	50	0	0	2	52
Control mean	PM	94	2	0	0	4	6
(n = 5)	PS	94	1	0	1	4	6
	DM	86	4	0	0	10	14
	DS	89	0	0	0	11	11

[1] 10 mg/kg/week. [2] Proximal motor nerve. [3] Proximal sensory nerve. [4] Distal motor nerve. [5] Distal sensory nerve.

Summary of Electrophysiological Studies in Patients

Motor and sensory conduction studies were normal in Case 1 (Table 9). Electromyography in this patient also showed normal motor unit potentials and a full interference pattern in all muscles. However, in the left flexor hallucis brevis and right triceps muscles spontaneous discharges of motor unit potentials were seen in the form of doublets, triplets and quadruplets. There were no fibrillation potentials or positive sharp waves. A regional curare test performed on the left limb produced only partial paralysis of the foot but a significant reduction in spontaneous muscle activity (fig. 7). No reduction in spontaneous activity was noted after blocking the posterior tibial nerve. The principal neurophysiological abnormalities in Cases 2 and 3 were mild to moderate slowing of sensory and motor conduction velocities and increased latencies (Table 9). Electromyography in Case 3 revealed an increased number of polyphasic potentials and a reduced interference pattern in gastrocnemius, extensor carpi radialis, abductor pollicis brevis and tibialis anterior. Positive sharp waves were also seen in the right gastrocnemius muscle and multiplets in the left gastrocnemius and left extensor brevis digitorum muscles. Electromyography of tibialis anterior and extensor digitorum brevis muscles in Case 2 revealed changes of denervation.

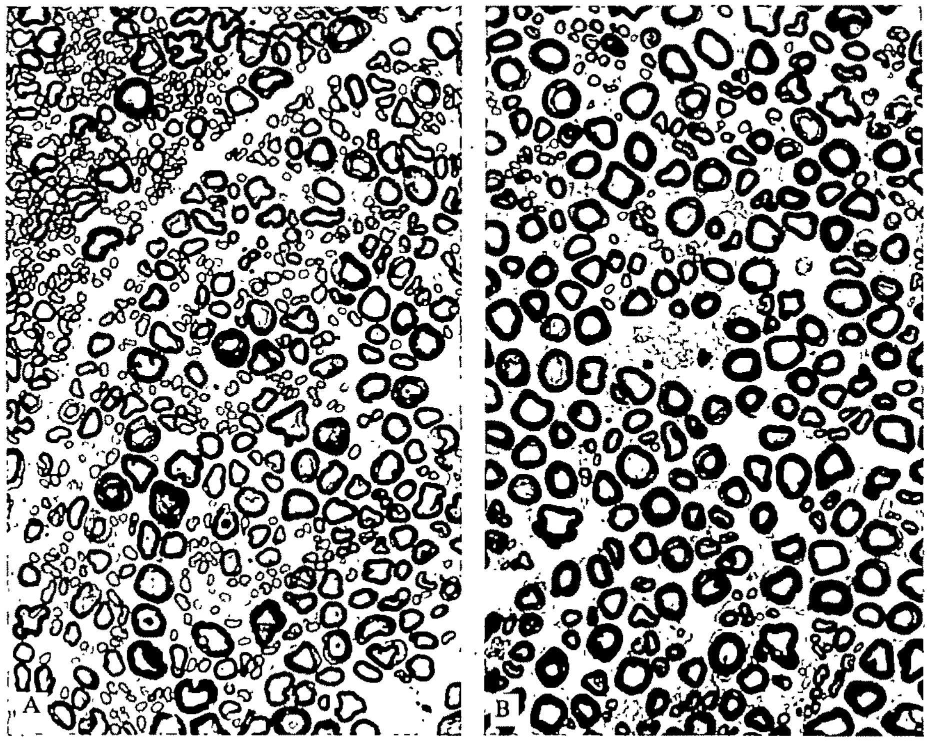

FIG. 6. Transverse section through ischiadic nerve from control (A) and gold-treated hens (B) showing a moderate depopulation of myelinated fibres following chrysotherapy.

TABLE 9. NERVE CONDUCTION STUDIES

	Motor conduction						*Sensory conduction*							
	Median		*Ulnar*		*Lateral popliteal*		*Median*			*Ulnar*			*Sural*	
Patient	*Latency* *ms*	*MCV* *m/s*	*Latency* *ms*	*MCV* *m/s*	*Latency* *ms*	*MCV* *m/s*	*Latency* *ms*	*Amplitude* *μv*	*CV* *m/s*	*Latency* *ms*	*Amplitude* *μv*	*CV* *m/s*	*Amplitude* *μv*	*CV* *m/s*
Case 1	4.0	50	3.4	58	4.8	48	3.2	20	50	2.3	20	52	22	46
Case 2	7.1	34	3.0	61	6.0	33	3.0	20	34	2.9	18	47	11	39
Case 3	5.7	41	4.9	50	13.7	23	3.4	16	39	3.0	14	33	22	31
Control mean	3.7	56	2.7	56	4.8	44	3.0	18	48	2.5	14	51	16	47
SD	0.5	6.0	0.4	4.6	0.5	5.1	0.3	7.5	3.7	0.3	6.5	3.8	6.5	3.7

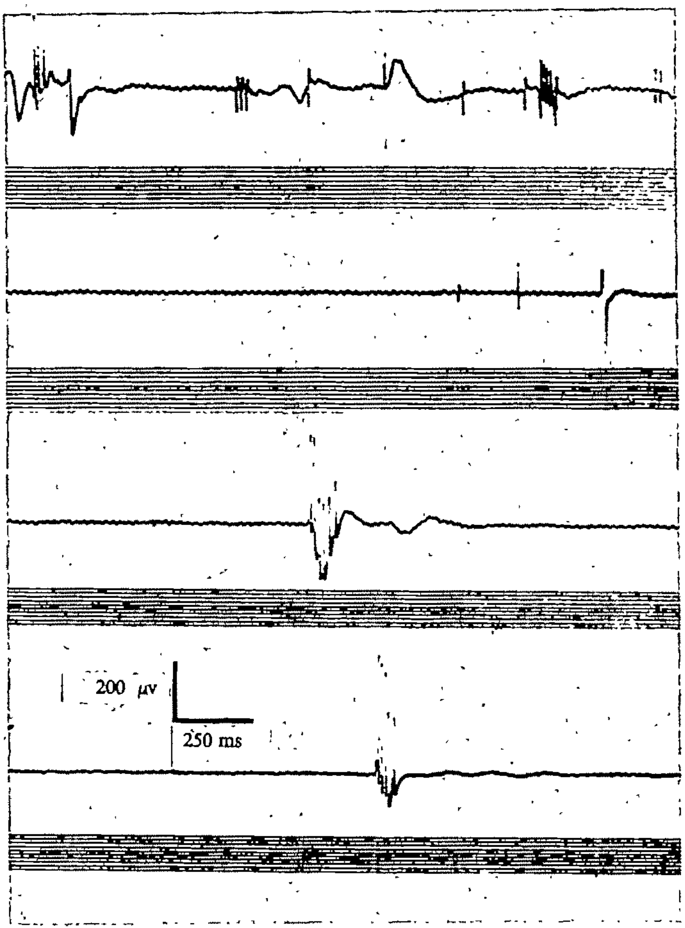

FIG. 7. EMG recorded from the left flexor hallucis brevis muscle at rest in Case 1. *Upper trace* shows irregular but continuous motor unit potential activity with multiplets. *Lower three traces* demonstrate a moderate reduction in spontaneous muscle activity after a regional incomplete curare block.

Animal Conduction Studies

In an analysis of variance carried out comparing onset and peak conductions and amplitudes in the three groups of hens there was found to be no significant variance between groups.

Blood Studies

Lymphocyte transformation studies with gold *in vitro* were negative in all three patients. While animal estimations of urea, hæmoglobin and packed cell volume were also normal, a marginal eosinophilia ($> 3 \times 10^9$/l) was present in 3 'low dose' and in 3 'high dose' hens.

DISCUSSION

Three patients are described who developed a symmetrical polyneuropathy while receiving intramuscular gold for the treatment of rheumatoid arthritis. In all patients, other causes of peripheral neuropathy such as alcoholism, uræmia, diabetes and porphyria were excluded. Their first symptoms were of symmetrical paræsthesiæ, two to six months after the onset of chrysotherapy. In one instance (Case 1) the neuropathy followed stomatitis, dermatitis and a marginal eosinophilia as a further manifestation of gold toxicity. Clinical findings in 2 cases suggested a predominant involvement of sensory fibres subserving pain and temperature. It was also noteworthy that a rapid clinical deterioration was seen in 2 patients in the first week and month, respectively, following cessation of gold therapy. Ultimately all 3 patients had a significant and sustained clinical improvement although the degree of recovery related to maximal disability. Previous reports of gold-induced neuropathy have also emphasized a rapidly progressive symmetrical polyneuropathy (Lescher, 1936; Hartfall, Garland and Goldie, 1937; Leiper, 1946; Doyle and Cannon, 1950; Endtz, 1958; Walsh, 1970). Radicular involvement has also been suggested by high CSF protein and the documentation of high spinal fluid gold levels, as in the present study.

A rapidly evolving mononeuritis multiplex with a high mortality may be seen in rheumatoid arthritis (Chamberlain and Bruckner, 1970). However, in this malignant rheumatoid syndrome there is both severe destructive joint disease and a widespread necrotizing arteritis. It is the global involvement of vasa nervorum which in some patients results in an interesting central fascicular degeneration of peripheral nerves in a watershed (mid-humeral and mid-femoral) distribution (Dyck, Conn and Okazaki, 1972). As might be expected with diffuse peripheral nerve ischæmia, there is electrophysiological evidence in this syndrome of widespread axonal degeneration. Unfortunately the vasculitis of rheumatoid disease is patchy and may not be present in biopsy samples. The present cases, however, differ in a number of respects: notably, in the symmetry of motor and sensory deficits, the absence of clinical evidence of vasculitis, the relatively quiescent rheumatoid disease and the favourable outcome. A predominantly sensory neuropathy has also been described in association with mild rheumatoid arthritis (Chamberlain and Bruckner, 1970). However, the severe motor deficits and the final rapid clinical progression in the present cases seem out of keeping with the negligible motor symptoms and the insidious course described in this type of rheumatoid neuropathy. Nor could the neurological findings in these patients be explained on the basis of compression or digital neuropathies (Scott, Hourihane, Doyle, Steiner, Laws, Dixon and Bywaters, 1961; Pallis and Scott, 1965).

Morphological and neurophysiological findings provided complementary evidence of peripheral nerve disease in all three patients. Thus segmental remyelination was seen in nearly 50 per cent of teased fibres in Case 3 with coefficients of variation of internodal length suggesting that this process predominated in the large nerve fibre population. While these morphological findings correlated with reduced motor and sensory conduction velocities there was in addition neurophysiological evidence of denervation. Both remaining patients had an increased incidence of axonal degeneration (type E) on teased fibre analysis with Case 2 showing a 16 per cent incidence of demyelination and remyelination. The latter finding is at the upper limit of control values, and taken in conjunction with reduced conduction velocities and normal amplitude of sensory action potentials suggests additional demyelinative pathology.

Walsh (1970), in the one previous histological study of gold neuropathy, also found evidence of both axonal degeneration and demyelination, but his patient had an abnormal glucose tolerance test so that the peripheral nerve morphology may have related to his diabetic state.

It is unclear whether the mechanism of production of neuropathy by gold is *via* direct toxicity or by an immunological reaction. Immunological mechanisms have been blamed for other types of gold toxicity (Gottlieb, 1977). Thus a type 1 hypersensitivity response has been thought to occur in some patients with cutaneous reactions to gold (Davis, Ezeoke, Munro, Hobbs and Hughes, 1973) and increased lymphocyte transformation to gold *in vitro* has been reported in patients with gold-induced blood dyscrasias (Denman and Denman, 1968). However, in only one patient reported here was the neuropathy associated with other features of gold toxicity. Lymphocyte transformation studies were also negative in all three patients, again adducing no evidence of an immunological basis for the neuropathy. While the tests were carried out in 2 patients, eighteen months and four years, respectively, after the onset of neuropathy, positive lymphocyte transformation to gold has been reported twelve years after reaction to the drug (Denman and Denman, 1968). On the other hand, the 2 patients who received the largest amounts of gold had the most severe neuropathies. Gold may cross the blood-brain barrier into the cerebrospinal fluid as demonstrated in Cases 1 and 3 and has previously been shown to reach the grey matter in appreciable amounts (Lescher, 1936). On balance it seems likely that the neuropathy in our patients was caused by a direct toxic effect of gold. This contention is further supported by the histological changes in motor and sensory nerves seeming to be dose-related in gold-treated hens. These animal studies also revealed a dual neuropathic pathology of axonal degeneration with segmental demyelination and remyelination, similar to that seen in the gold-treated patients. The absence of a significant alteration in motor nerve conduction in gold-treated hens may result from the relative insensitivity of maximum motor conduction studies which are frequently unaffected in mild peripheral neuropathies (Hopf and Eysholdt, 1978). While the combined peripheral nerve pathology in patients and hens could represent a toxic effect of gold on both the cyton and its Schwann cells an alternative possibility is that demyelination in gold neuropathy is secondary to a primary axonal degeneration, similar to that seen in uræmia (Dyck, Johnson, Lambert and O'Brien, 1971). It was to explore the possibility of a primary atrophy of peripheral nerve axons exposed to gold that a regression analysis of myelin lamellæ on axonal area was undertaken. Neither the slope of regression lines, standard deviation of residuals nor intercepts supported the concept of a secondary demyelination in gold neuropathy.

Although gold neuropathy clinically resembles a dying-back process, the distribution of pathology in the hen appears unrelated to the length of axons. Rather the degeneration is suggestive of a multifocal attack. Spencer and Schaumburg (1977) have also recently found non-dying-back neuropathies with the peripheral nerve toxins n-hexane and methyl-n-butyl ketone.

Myokymia (literally wave of muscle) was an interesting finding in two patients and in Case 1 was a predominant part of the neurological illness. The movements were typically constant, coarse, slow and undulating and quite distinct from the darting irregular twitches of fasciculations. The distribution was remarkably fluid in one case and sharply localized in another. Myokymia has been previously shown to involve only isolated portions of a few muscles (Sarova-Pinchas, Goldhammer and Braham, 1978).

It is of interest that there are reports of movements typical of myokymia in gold-treated patients in the early French literature. Thus Chavany and Chaignot (1934) describe generalized fibrillary twitchings affecting the whole body with the exception of the tongue and facial muscles. Identical cases were subsequently reported by Dujardin (1944) and Garcin, Kipfer and Pestel (1945). Only recently in the English literature has Furst and co-workers (1977) reported 'diffuse fasciculations' in a patient receiving gold and Meyer, Haecki, Ziegler, Forster and Schiller (1978) documented generalized myokymia in two gold-treated patients.

The clinical suspicion of myokymia requires neurophysiological confirmation. Two types of electromyographic pattern have been described: spontaneous continuous trains of repetitively firing motor unit potentials (Gamstorp and Wohlfart, 1959; Gardner-Medwin and Walton, 1969) or a regular repetition of groups of from 2 to over 200 motor units forming 'multiplets' (Denny-Brown and Foley, 1948; Harman and Richardson, 1954). In some the electromyograph may be characterized by both continuous trains of spontaneous potentials and by multiplets (Williamson and Brooke, 1972). Although myokymia has been associated with diverse lesions, both centrally (Frohmann, 1906; Lambert, Lover and Mulder, 1961; Matthews, 1966; Espinosa, Lambert and Klass, 1967) and peripherally (Wallis, Van Poznak and Plum, 1970; Valenstein, Watson and Parker, 1978) in the nervous system, and described in normal individuals in states of debility and fatigue, it is noteworthy in the present context that it has also resulted from the ingestion of other peripheral nerve toxins, namely, lead (Neumark, 1920) and 2-azarindinyl ethanol (Zager, McCarty and Standaert, 1969).

There have been detailed electrophysiological studies of myokymia of peripheral nerve origin (Isaacs, 1961; Gardner-Medwin and Walton, 1969; Wallis *et al.*, 1970; Welch, Appenzeller and Bicknell, 1972; Black,Garcia-Mullin, Good and Brown, 1972; Isaacs and Heffron, 1974; Irani, Purohit and Wadia, 1977). Most authors agree that it is due to peripheral nerve hyperexcitability at a site just proximal to the myoneural junction. Though the peripheral nerve has been unequivocally implicated in its genesis there are few histological studies of peripheral nerve in myokymia. Previous findings have consisted of degenerative changes in a few nerve fibres (Wallis *et al.*, 1970) degeneration with patchy demyelination (Welch *et al.*, 1972) and normal findings (Isaacs and Heffron, 1974; Irani *et al.*, 1977). The two patients whose myokymia was associated with sensory symptoms and signs had different histological abnormalities of axonal degeneration and demyelination on sural nerve biopsy. Present evidence suggests there is no constant peripheral nerve pathology correlating with myokymia.

It is possible that gold neuropathy may not be as rare as previously thought (Hartfall *et al.*, 1937; Walsh, 1970; Gottlieb, 1977). In the period during which these three cases of gold neuropathy were encountered in Dunedin, there were only three patients identified with serious gold-induced thrombocytopenia (less than $50 \times 10^9/l$) although the latter is usually regarded as one of the commoner major complications of gold therapy (Gottlieb, 1977).

Finally, it is pertinent that in two of our patients with gold neuropathy minor paræsthesiæ preceded severe neurological disability by three and seven months. It is clear that in the clinical monitoring of gold-treated patients great importance must be given to such minor neuropathic symptoms. The present study suggests that myokymia may be one factor which will help to differentiate gold-induced from rheumatoid neuropathy. In its absence the differential diagnosis may be difficult and only settled by cessation of chrysotherapy.

SUMMARY

Three cases of gold-related neuropathy are reported. Clinical features include an acute, symmetrically progressive polyneuropathy, focal or generalized myokymia and a tendency for initial neurological deterioration followed by improvement, after cessation of chrysotherapy. The degree of clinical recovery related to maximal disability. Morphological findings on sural nerve biopsies revealed both axonal degeneration and segmental remyelination.

Similar peripheral nerve histology was seen in a parallel animal study in which the severity of the neuropathy was dose-related.

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HEREDITARY LEUCODYSTROPHY IN THE MOUSE: THE NEW MUTANT TWITCHER

by L. W. DUCHEN, EVA M. EICHER, JEAN M. JACOBS,
F. SCARAVILLI *and* FERNANDA TEIXEIRA

(*From the Department of Neuropathology, Institute of Neurology, The National Hospital, Queen Square, London WC1 and The Jackson Laboratory, Bar Harbor, Maine, USA*)

INTRODUCTION

INHERITED neurological disorders in laboratory animals provide models for the study of the ætiology and pathogenesis of disease states in the nervous system. The interest in a mutant becomes the greater the more its pathology resembles that of a human disease. This paper reports a new neurological mutant mouse in which the pathology of the central nervous system and of the peripheral nerves is identical to that described in Krabbe's disease, an inherited ('globoid cell') leucodystrophy in man.

In 1976 two mice showing behavioural abnormalities were noted in one litter of CE/J mice in the Animal Resource Division of the Jackson Laboratory. Matings established between normal animals of that litter resulted in the recovery of the deviant phenotype in equal numbers of males and females in the next generation indicating the presence of a new autosomal recessive mutation. This mutation was named twitcher and the gene symbol *twi* allotted to it.

MATERIAL AND METHODS

Animals

Matings between heterozygous mice, which appear normal, produce approximately 25 per cent of homozygous (*twi*/*twi*) offspring which will show evidence of the disease. Maintaining the *twi* mutation involves the mating of apparently normal mice which have twitcher littermates. On the average 4 out of 9 such matings will produce affected young.

Because mice of the CE/J strain are poor breeders, the *twi* allele was placed on to another genetic background. A heterozygous twitcher (+/*twi*) CE/J male was mated to a C57BL/6J female and their F_1 offspring intercrossed to produce *twi* breeding stock. Mice of the F_2 generation were sent to England in April 1977 and the morphological and behavioural studies reported here were made on offspring from these mice. The *twi* mutant allele has since been introduced twice more on to the C57BL/6J inbred strain at the Jackson Laboratory where the linkage analysis reported in this paper was conducted.

In order to find the chromosomal location of the *twi* locus, linkage experiments have been conducted by mating known heterozygous +/*twi* individuals to *Mus musculus castaneus* mice, and the F_1 (+/+ or +/*twi*) individuals backcrossed to known +/*twi* individuals of the *twi* stock. All *twi*/*twi* offspring were classified for a number of isozyme loci known to be segregating. In addition, homozygous *twi*/*twi* mice produced from the original matings of (CE/J × C57BL/6J)F_1-+/*twi* × same were analysed for several segregating loci. Finally, several matings were established between individuals segregating several dominant mutations and *twi* and all *twi*/*twi* offspring were classified for the presence of the dominant mutations. The specific loci used in the above experiments are listed in the Results section.

Light Microscopy

Numerous mutants and their normal littermates ranging in age from 30 to 60 days were perfused under pentobarbitone anæsthesia with formo-calcium (1 per cent calcium acetate in 10 per cent formalin). After decalcification in formic-citrate, blocks were taken from head, trunk and limbs for embedding in paraffin wax or for frozen sections. Much use was made of the serial-block technique of embedding (Beesley and Daniel, 1956) which facilitates the study of many different levels of brain, spinal cord and limb muscles. Routine histological methods of staining were used including silver impregnation of axons, luxol fast blue with cresyl violet (Klüver and Barrera, 1953), periodic acid-Schiff (PAS), acid cresyl violet for metachromasia in frozen as well as paraffin sections and oil red O for neutral fat in frozen sections.

Electron Microscopy

Under pentobarbitone anæsthesia mutants and normal littermates were perfused through the left ventricle with 3 per cent glutaraldehyde and 1 per cent paraformaldehyde in cacodylate-buffer, pH 7.3 at 4° C. After overnight fixation blocks were taken from many regions of cerebral and cerebellar hemispheres, medulla, spinal cord, optic nerves, gasserian and dorsal root ganglia, motor and sensory roots, peripheral nerves and skeletal muscles. After post-fixation in 2 per cent osmium tetroxide, tissues were dehydrated and embedded in epoxy resin. Sections at 1 μm were stained with toluidine blue to facilitate orientation and trimming of blocks. Ultrathin sections were stained with uranyl acetate and lead citrate.

RESULTS

Linkage

In order to find the chromosomal location of the *twi* locus, several different matings were established that segregated for *twi* and for two or more other loci. Unfortunately, linkage tests with the following chromosomally assigned loci were negative (Chr = chromosome): Chr 1 *Id-1* (isocitrate dehydrogenase-1), *Dip-1* (dipeptidase-1); Chr 2*a* (non-agouti); Chr 3 *Car-1* (carbonic anhydrase-1), *Car-2* (carbonic anhydrase-2), *Amy-1* (amylase-1); Chr 4 *Gpd-1* (hexose 6-phosphate dehydrogenase); Chr 5 W^v (viable dominant spotting); Chr 6 Mi^{wh} (white), Chr 7 *Gpi-1* (glucose phosphate isomerase-1), c^e (extreme dilution), *Hbb* (β-chain hæmoglobin); Chr 9 *Mpi-1* (mannose phosphate isomerase-1), *Mod-1* (malic enzyme, supernatant); Chr 14 *Np-1* (nucleoside phosphorylase-1); Chr 15 *Gpt-1* (glutamate pyruvate transaminase-1), *Gdc-1* (NAD α-glycerol phosphate dehydrogenase); Chr 17 *Pgk-2* (phosphoglycerate kinase-2); and Chr 19 *Got-1* (glutamate oxalate transaminase, soluble). Further linkage studies are in progress.

The Clinical Syndrome

Homozygous *twi* mice are apparently normal at birth and prior to the appearance of clinical signs, are indistinguishable from their normal littermates, some of which are heterozygous for the *twi* allele (*twi*/+) and some homozygous +. Evidence of disease usually appears at about the thirtieth day. Early signs include a body weight lower than normal, which becomes more marked until there is very obvious wasting of trunk and limbs, and a tremulousness, which is generalized but particularly marked in the head. Although limb movements and grooming are normally co-ordinated, mutants are less active than their unaffected littermates. Soon after the appearance of signs of abnormality, progressive muscular weakness becomes evident, affecting the hindlimbs more than the forelimbs. Later the head is held low indicating weakness of neck muscles. The hindlimbs are placed more laterally than normal during walking but in advanced stages of the disease they may become paralysed and are dragged behind the body. In late stages there is a dorsal kyphosis producing a hump in the lower cervical-upper thoracic region. The disease progresses inexorably and although survival can be prolonged by careful husbandry, no mutant has lived for longer than three months.

Pathology of the Central Nervous System

The pathological changes in the central nervous system (CNS) were found mainly in the white matter. Patchy areas of myelin loss were present throughout the CNS but affected the spinal cord (fig. 1) and brain-stem with particular severity. In all

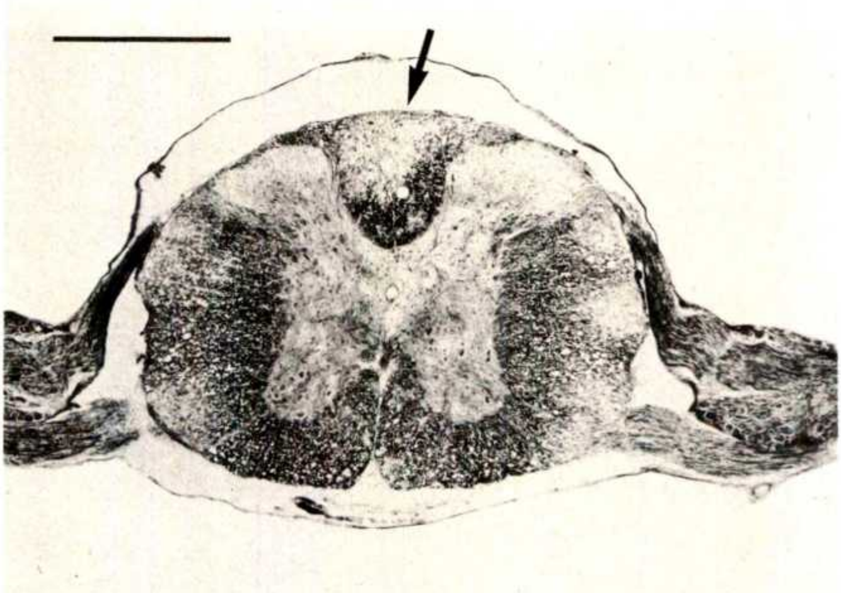

FIG. 1. Section of thoracic spinal cord of a 2-month-old twitcher. The white matter shows patchy myelin loss which is particularly marked in the dorsal columns (arrow). Luxol fast blue and cresyl violet. Bar = 0.5 mm.

affected areas of white matter there were many abnormal cells lying singly or in clusters around vessels. Many of the cells (fig. 2) were multinucleated. They measured up to about 30 μm in diameter and contained abundant foamy cytoplasm which stained weakly with the PAS reaction (resistant to amylase), was not metachromatic with acid cresyl violet and did not contain neutral fat. There was a mild astrocytic gliosis in areas of myelin loss and axons were demonstrated with silver impregnation. No significant abnormalities were seen in grey matter with light microscopy.

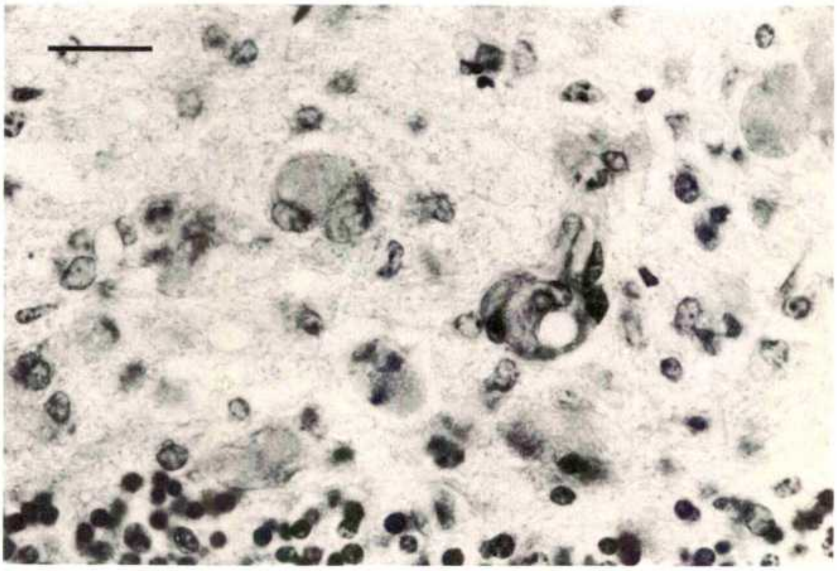

FIG. 2. Section of cerebellum of a 2-month-old twitcher showing an affected area of white matter. Large multinucleated cells with abundant PAS-positive cytoplasm are present. PAS and hæmatoxylin. Bar = 20 μm.

Electron microscopic studies were made mainly of severely affected areas of white matter of medulla and spinal cord. In all these areas some degenerating axons, myelin debris and abnormal cells were present. These cells contained crystalloid bodies and membrane-bound inclusions which were pleomorphic and were either homogeneous or had an irregularly striated appearance or contained filaments and tubules. Two different types of tubule were seen, the smaller measuring approximately 13 nm in diameter and the larger, 35 nm in diameter, some of which were apparently twisted at 200 nm intervals (fig. 3). Some cells identified as oligodendrocytes and astrocytes contained inclusions which were small and membrane-bound, round or oval in shape, and composed of lipid-like material with a variable electron density (figs. 4 and 5).

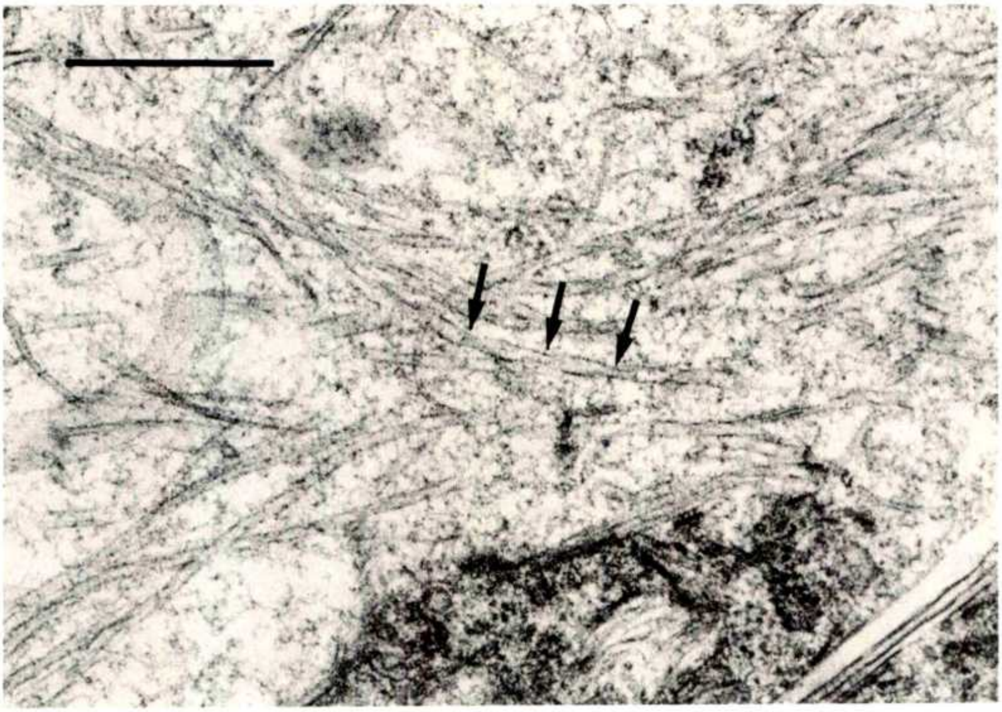

FIG. 3. Electron micrograph of cerebral cortex of a twitcher shows part of a macrophage. Tubules 35 nm wide and twisted at approximately 200 nm intervals (arrows) are shown. Bar = 0.5 μm.

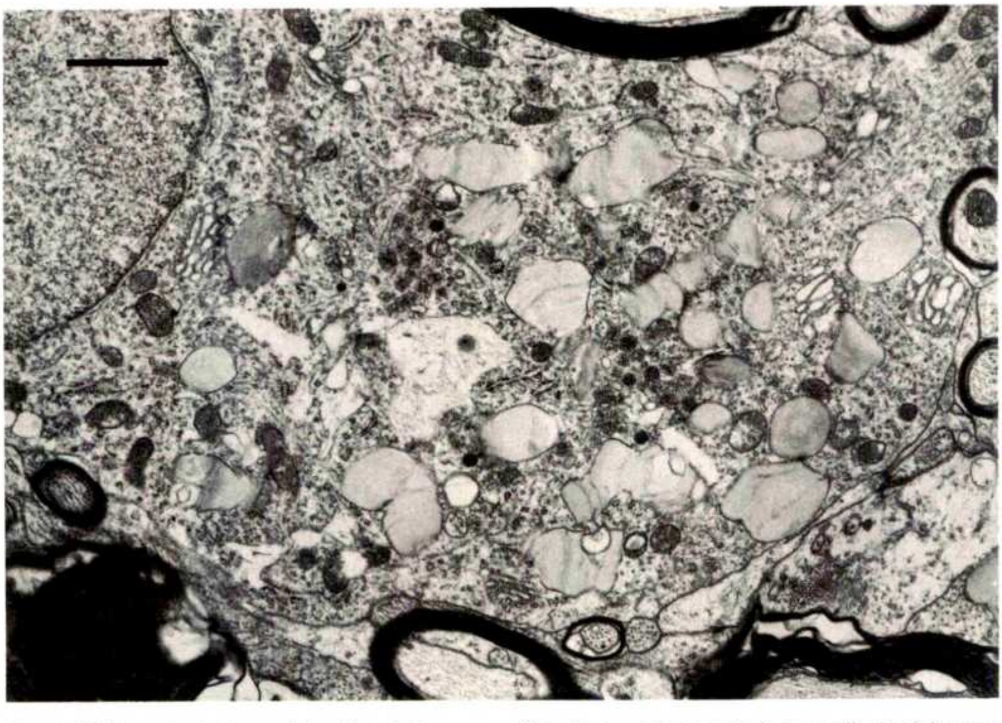

FIG. 4. White matter in the medulla of a twitcher mouse. This electron micrograph shows a cell containing many membrane-bound inclusions. The cell is closely associated with myelinated fibres, one of which is degenerating, and is probably an oligodendrocyte. Bar = 1 μm.

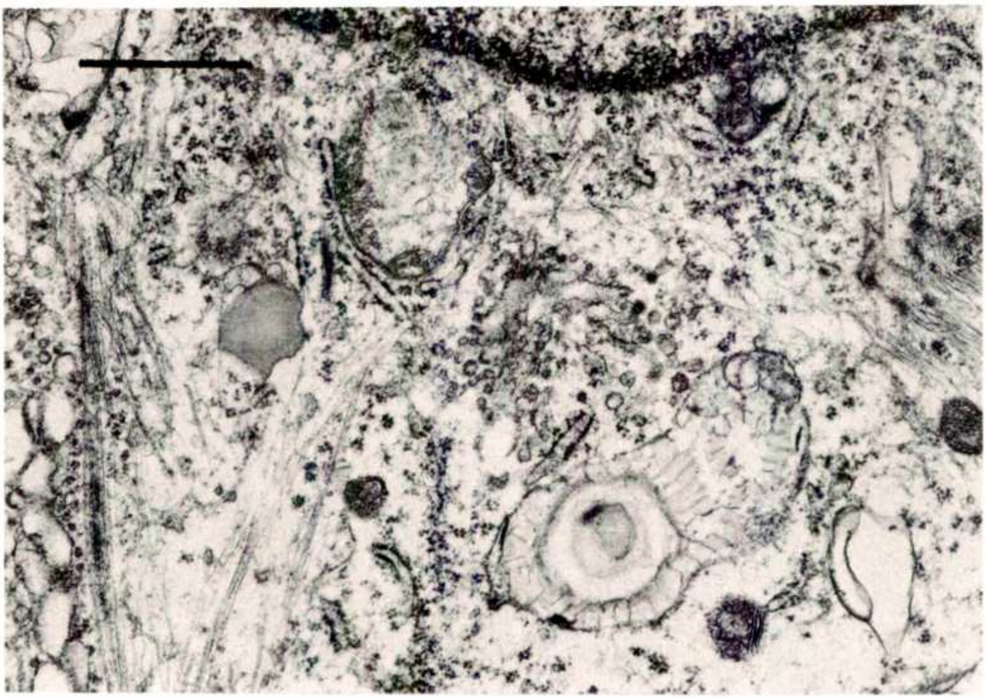

FIG. 5. In the white matter of the medulla of an affected mouse an astrocyte with glial filaments contains an irregular membrane-bound inclusion composed of electron-lucent material with a striated appearance. Bar = 1 μm.

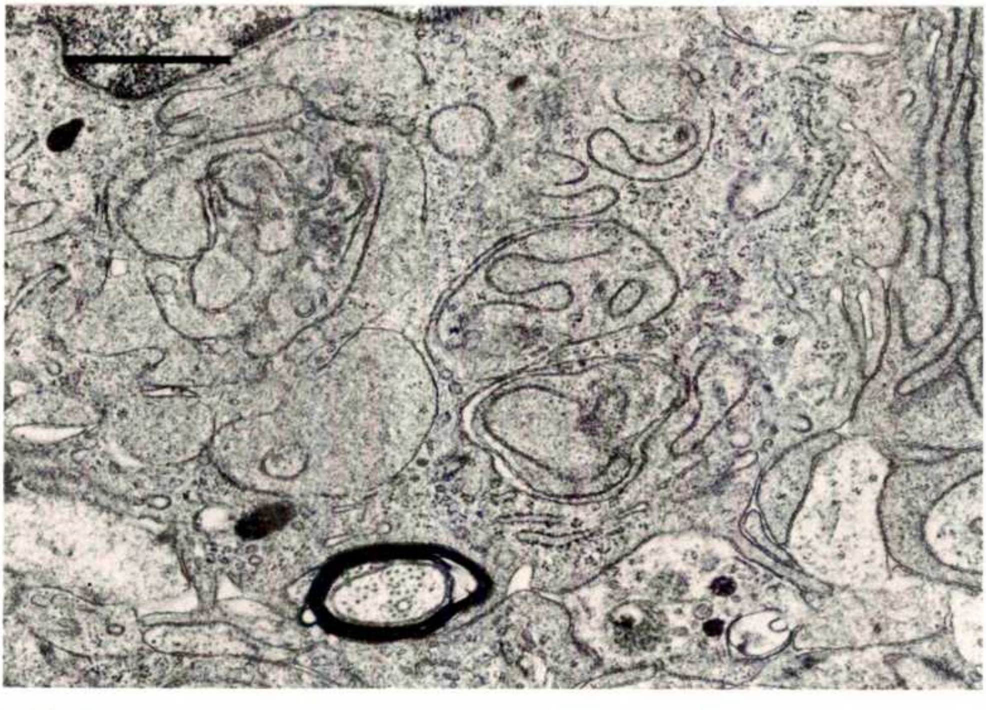

FIG. 6. Electron micrograph showing part of an abnormal cell, probably an oligodendrocyte, in the white matter of a twitcher. This cell shows highly complex infoldings containing finely granular material. Bar = 1 μm.

In the areas of abnormal white matter a further type of cell was seen that differed from those described above. These cells (fig. 6) showed complex interdigitating cytoplasmic processes and were also associated with myelinated axons, features which suggest an oligodendroglial origin. They did not contain inclusions. Cells with this appearance are not normally found in white matter and their nature is unknown. They may represent abortive attempts at myelination by oligodendrocytes. In the perikarya of some nerve cells there were membrane-bound bodies up to 1 μm diameter which contained finely granular material (fig. 7A). Less commonly seen were aggregations of granules each surrounded by an electron lucent halo (fig. 7B). These aggregations were not membrane-bound. The majority of dorsal root ganglion cells contained bodies frequently bounded by a double membrane and filled with either irregularly striated or lamellated material. These bodies were probably of mitochondrial origin. None of the inclusions described here are normally seen in neuronal perikarya.

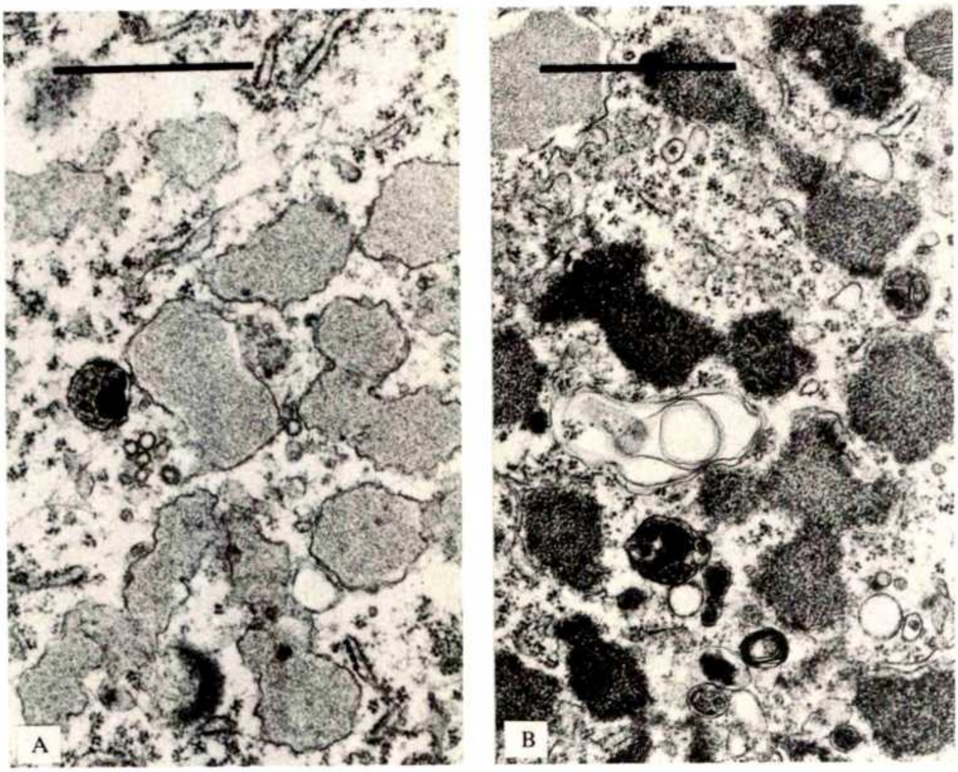

FIG. 7. Inclusions in motor nerve cells in medulla of a twitcher. A, membrane-bound bodies are filled with finely granular material, which resembles that seen in cisternæ of rough endoplasmic reticulum. Bar = 1 μm. B, non-membrane-bound inclusions are composed of coarse granules surrounded by a clear halo. In addition, some multivesicular bodies can be seen. Bar = 1 μm.

The Pathology of Peripheral Nerves

Peripheral nerves and nerve roots were clearly abnormal macroscopically, appearing thickened, pale and translucent. In all peripheral nerves, axons were demonstrable by silver impregnation and little or no axonal degeneration was evident. However, axons were widely separated from each other by numerous abnormal cells (fig. 8) similar to those seen in areas of myelin loss in the CNS and including multinucleated forms. Transverse sections of plastic-embedded nerves showed few normally myelinated nerve fibres. Myelin sheaths were degenerating or were abnormally thin, indicating remyelination, and many axons were demyelinated (fig. 9). Although quantitative studies have yet to be made axonal numbers were not obviously reduced.

Electron microscopy showed myelin sheaths in various stages of breakdown, some associated with an axon distorted in shape but otherwise normal. Demyelinated axons or axons showing early remyelination were numerous (fig. 10).

Although there was little evidence of degeneration of unmyelinated fibres, some had an abnormally elliptical shape in transverse sections, associated with excessively long mesaxons (fig. 11). Schwann cell cytoplasm surrounding some unmyelinated fibres was unusually electron-lucent while attenuated Schwann cell processes probably represented unmyelinated fibres in which the axons had degenerated. Schwann cells associated with both degenerating and apparently normal myelinated fibres also appeared swollen and electron-lucent and some contained inclusions composed of filaments, tubules or membranous material (fig. 12).

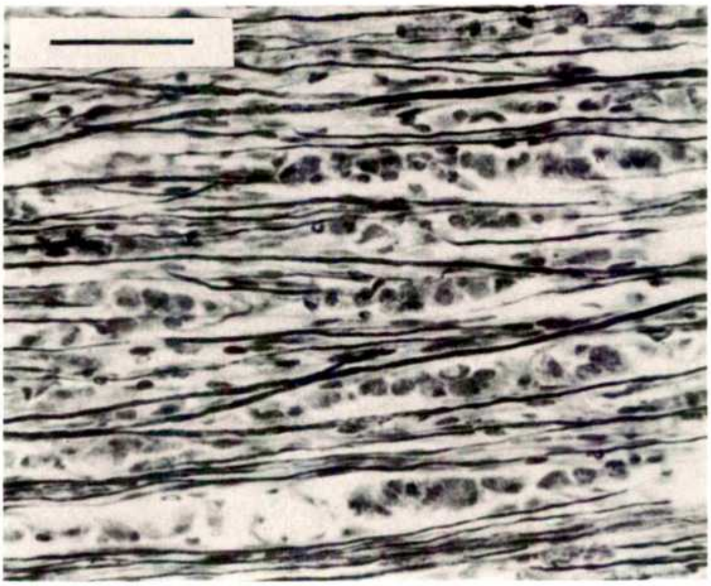

FIG. 8. Longitudinal section of sciatic nerve of a 49-day-old twitcher. Axons are intact but are separated by large numbers of macrophages. Glees and Marsland silver method. Bar = 50 μm.

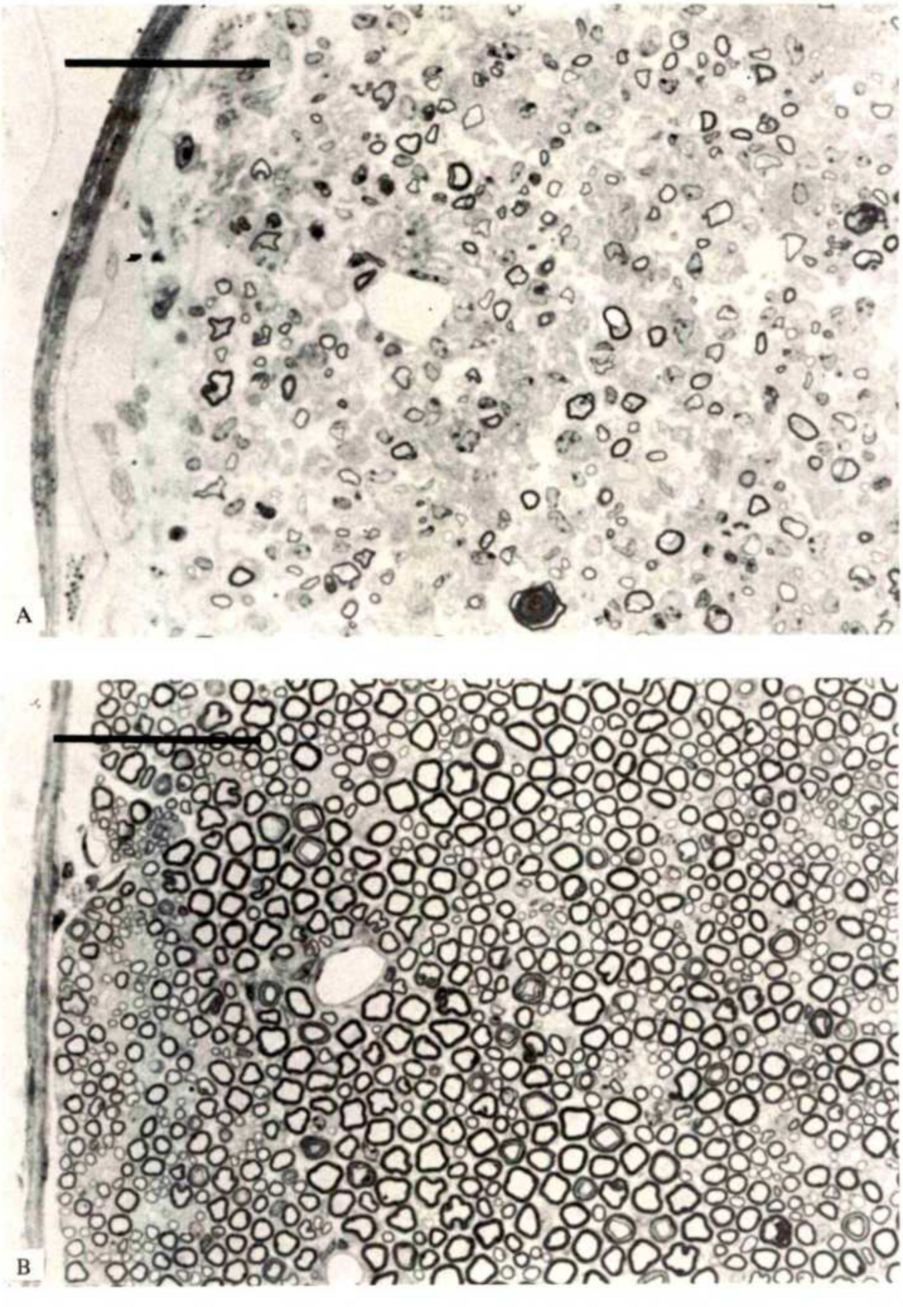

FIG. 9. Transverse sections of sciatic nerve of a 48-day-old twitcher. A, showing myelin degeneration, demyelinated axons and fibres with abnormally thin myelin sheaths. Many macrophages lie between the nerve fibres and there is marked subperineurial œdema. B, nerve from a normal mouse of the same age. 1 μm araldite sections stained with toluidine blue. Bar = 50 μm.

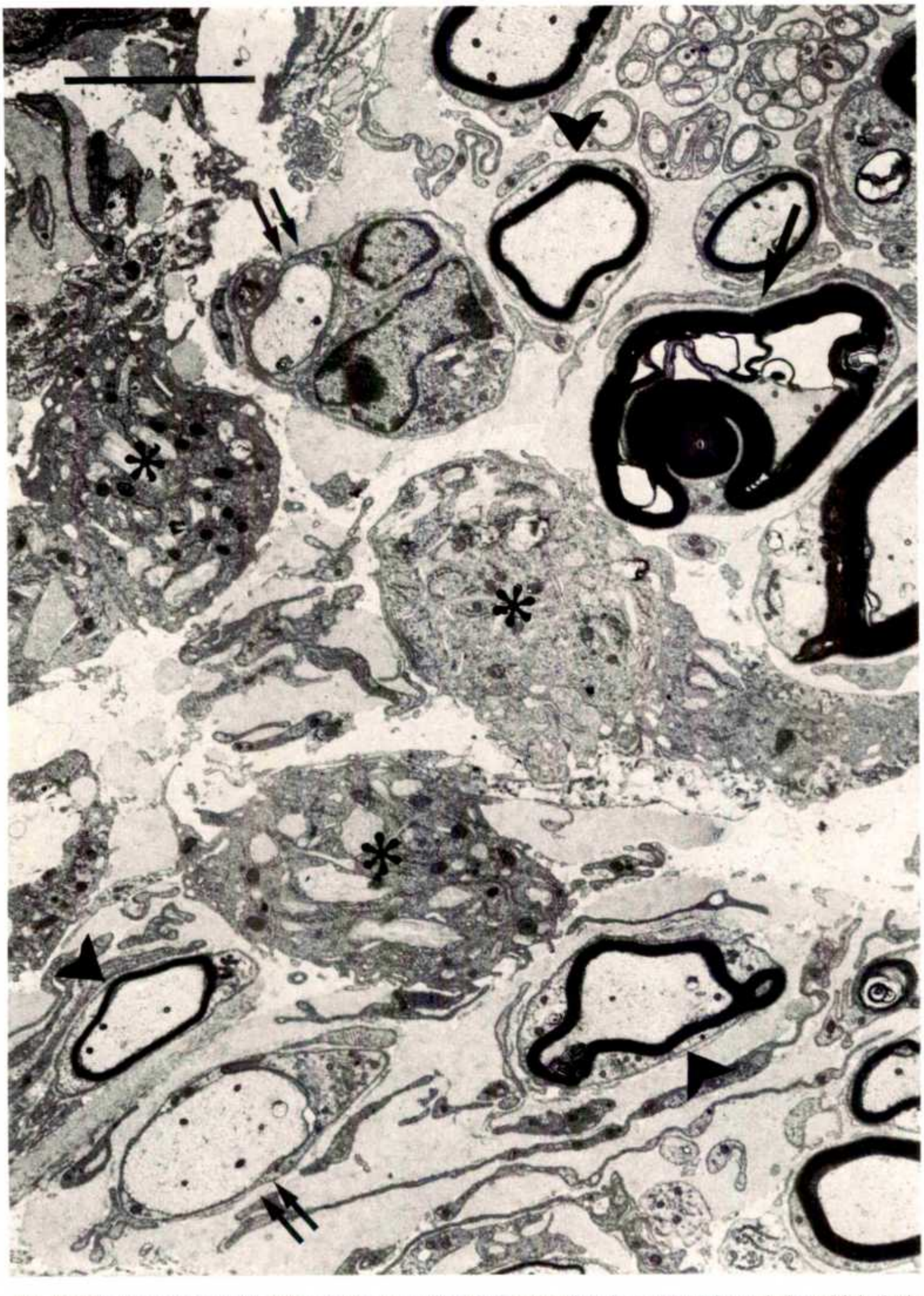

FIG. 10. Electron micrograph of the sciatic nerve of a twitcher showing three macrophages laden with inclusions (asterisks). The myelin sheath of one fibre (arrow) shows early degeneration while the axon, although distorted in shape, is otherwise normal. Two demyelinated axons are shown (double arrows). Some axons have inappropriately thin myelin sheaths and are probably being remyelinated (arrow-heads). There is endoneurial œdema and excess collagen. Bar = 5 μm.

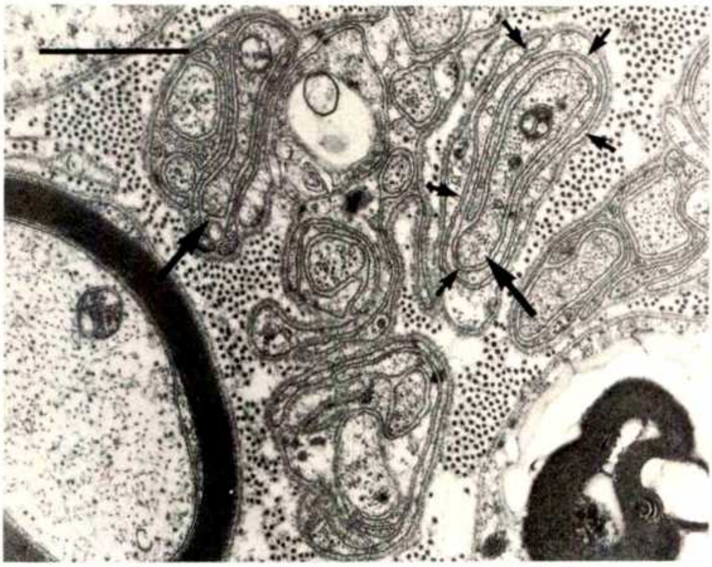

FIG. 11. In a transverse section of the sciatic nerve, some unmyelinated fibres are abnormally shaped (big arrows), and have unusually long mesaxons (small arrows). Bar = 1 μm.

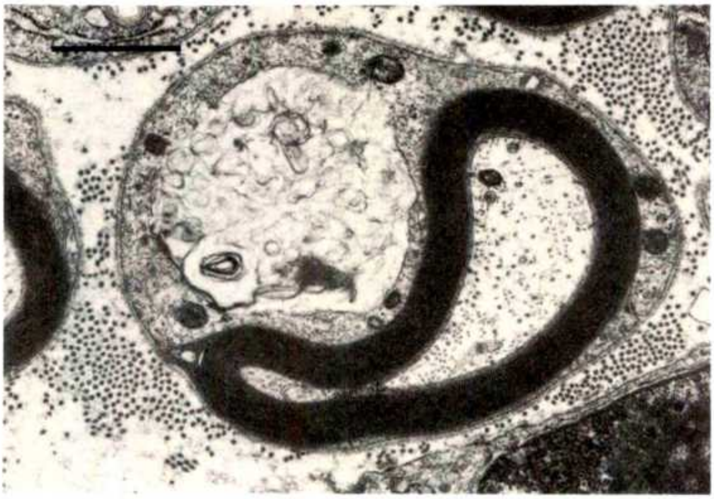

FIG. 12. The Schwann cell of this myelinated nerve fibre contains a large membrane-bound inclusion while the axon and myelin sheath appear normal. Bar = 1 μm.

The abnormal cells lying among nerve fibres had the characteristics of macrophages and contained many inclusions. Some consisted of lamellar material. The most common inclusions resembled the large membrane-bound bodies described in the abnormal cells in the CNS. Within these bodies there were multi-angulated structures of varying shape (fig. 13) as well as twisted tubules. In addition there were apparently 'empty' needle-shaped structures. Numerous eosinophils were seen in the interstitium of peripheral nerves.

DISCUSSION

The clinical and pathological findings in the new mutant mouse twitcher point to a genetically induced disorder primarily affecting myelin in both the central nervous system and peripheral nerves. A prominent feature in both central and peripheral nervous systems is the presence of large macrophage-like cells with cytoplasmic inclusions. Some of these inclusions are non-specific but the twisted tubules and multi-angular inclusions are highly characteristic of this disease. Inclusions in nerve cells of both CNS and sensory ganglia differed from those in macrophages, were probably derived from perikaryal organelles and suggest a metabolic disturbance.

Abnormal Schwann cells with inclusions and swollen watery cytoplasm were associated with apparently normal myelinated fibres. It seems that these Schwann cell changes precede the breakdown of myelin which appears to have been formed normally. However, it is possible that myelin breakdown may be taking place at another level of the same internode, out of the plane of section.

This new inherited disease of the nervous system in the mouse seems to belong to the group of leucodystrophies which includes a variety of disorders of myelin metabolism. Other leucodystrophies have been described in mutant mice. In the jimpy (*jp*/*Y*) mouse there seems to be an abnormality mainly affecting oligodendrocytes. The myelin defect is considered to be the result of an absence of myelination rather than a breakdown of myelin (Farkas-Bargeton, Robain and Mandel, 1972). Fine structural studies showed lipid inclusions in oligodendroglial cells before there is any appreciable accumulation of myelin in the spinal cord (Meier, Herschkowitz and Bischoff, 1974). These inclusions do not resemble those found in the twitcher mouse and neither is the peripheral nervous system affected in jimpy (Sidman, Dickie and Appel, 1964; Sidman, 1965; Hogan, Joseph and Schmidt, 1970; Herschkowitz, Vassella and Bischoff, 1971; Hogan, 1977).

The mutant myelin synthesis deficiency shows hypomyelination with no evidence of breakdown of myelin (Meier and MacPike, 1970). However, this mutant is probably not a specific entity since it was found to be allelic with jimpy and its gene symbol redesignated jp^{msd} (Eicher and Hoppe, 1973).

In the quaking (*qk*/*qk*) mouse the disorder is considered to be a leucodystrophy in which a decreased synthesis of cerebroside results in a deficit of myelin lipids (Baumann, Jacque, Pollet and Harpin, 1968; Hogan and Joseph, 1970; Costantino-Ceccarini and Morell, 1971). Morphological studies have shown hypomyelination

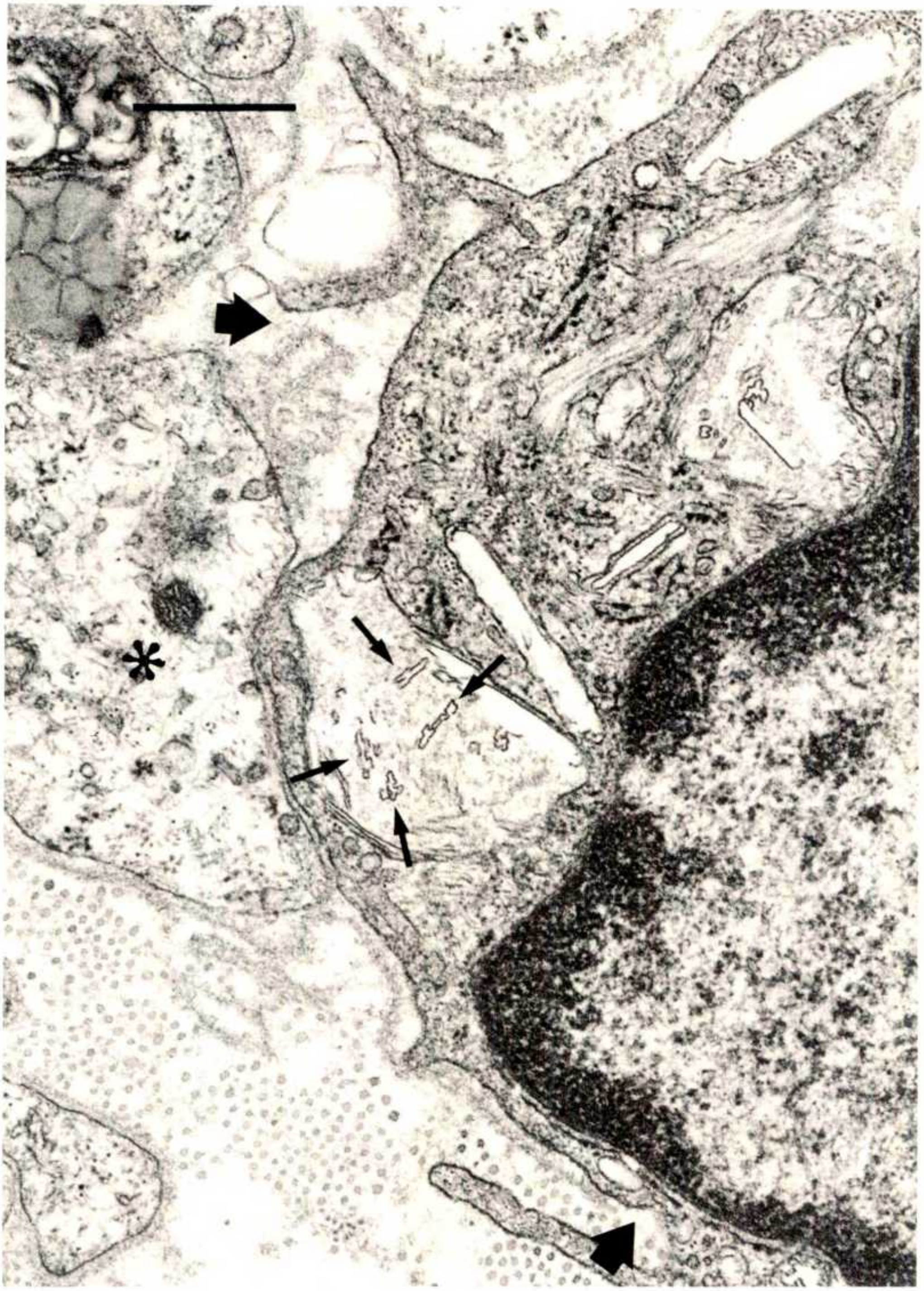

FIG. 13. An inclusion containing multiangular bodies (arrows) is seen in a macrophage in the sciatic nerve. This cell is invading a demyelinated nerve fibre. A Schwann cell process is indicated by an asterisk. Rupture of the basement membrane is shown at the thick arrows. Bar = 0.5 μm.

but no evidence of myelin degeneration (Wiśniewski and Morell, 1971; Friedrich, 1974).

Genetically determined human leucodystrophies include sudanophilic, metachromatic and globoid cell leucodystrophy (Krabbe, 1916). The inclusions found in the twitcher mouse are neither sudanophilic nor metachromatic. However, there are a number of features common to both the mutant twitcher and human globoid cell leucodystrophy including the characteristic large cells containing PAS-positive material (Blackwood and Cumings, 1954) and the crystalline, tubular and multi-angular inclusions found electron microscopically (Shaw and Carlson, 1970; Schochet, McCormick and Powell, 1976; Brownstein, Meagher-Villemure, Polomeno and Little, 1978). All these types of inclusion have been described by Yunis and Lee (1976) in two Cairn terriers affected by globoid cell leucodystrophy and similar structures have also been produced experimentally in rats by the intracerebral injection of galactocerebroside (Austin and Lehfeldt, 1965; Olsson, Sourander and Svennerholm, 1966; Andrews and Menkes, 1970).

In the twitcher mouse the involvement of peripheral nerves by demyelination, remyelination and the presence of macrophages with inclusions is another important similarity to human globoid cell leucodystrophy (Sourander and Olsson, 1968; Dunn, Lake, Dolman and Wilson, 1969; Bischoff and Ulrich, 1969; Lyon, Jardin and Aicardi, 1971; Schlaepfer and Prensky, 1972). Sourander and Olsson (1968) concluded that the peripheral neuropathy in the human disease is part of the primary disturbance and they also observed evidence of axonal degeneration with light microscopy. Other authors have not observed evidence of axonal degeneration in peripheral nerves in human cases and our present studies show that this does not occur to any significant extent.

Since the leucodystrophy in the twitcher mouse so closely resembles Krabbe's disease in man, the mutant could provide a useful model for the study of the pathogenesis of this myelin sheath abnormality.

SUMMARY

A new inherited neurological disease in the mouse (the mutant twitcher) has been studied. Transmission is by an autosomal recessive gene (*twi*). Affected animals are apparently normal at birth but develop a generalized tremor at about 3 weeks of age followed by progressive weakness and wasting. The disease is fatal by 3 months.

The principal pathological changes affect the myelin of both central and peripheral nervous systems. Degeneration of myelin sheaths and the presence of multinucleated macrophages with PAS-positive cytoplasm are characteristic findings. Peripheral nerves show remyelination following demyelination. Electron microscopically the macrophages contain a variety of inclusions in which there are crystalline and multi-angular structures and twisted tubules. The abnormalities closely resemble those found in globoid cell leucodystrophy (Krabbe's disease) in man.

ACKNOWLEDGEMENTS

We should like to thank R. Pinkham, who found the first twitcher mouse at the Jackson Laboratory; Janan Eppig, Sally Fox and Henry Goulding for their help in the maintenance of the animals and linkage analysis; Rosemary Bowden and Jenny Grainger for the microscopic preparations and J. A. Mills for the photographs. F.T. is in receipt of a WHO Fellowship. This research was supported by grants from NIH (RR 01183 and NS 09378), the Brain Research Trust and the National Fund for Research into Crippling Diseases. The Jackson Laboratory is fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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NOTICES OF RECENT PUBLICATIONS

Sherrington: His Life and Thought. By J. C. Eccles and W. C. Gibson, 1979. Pp. 290. Berlin, Heidelberg, New York: Springer International. Price DM 34.00.

This attractive volume is the long awaited first comprehensive biography of Professor Sir Charles Sherrington, whose death in 1952 brought to a close almost ninety-five years of a most active life that spanned an unprecedented growth of physiology, medicine and science. His contribution to the physiology of the nervous system revolutionized that subject and gained him an international reputation at an early age. Though several brief memoirs have previously appeared, little was known of Sherrington's early life until a privately circulated account of the Beaumont Lecture by his son, Carr Sherrington, was made in 1957. The recent release of original material by Carr and Margaret Sherrington and others to the authors of this book has now enabled this more ample biography. The many facets of the long life of this most profound scholar, linguist and scientist are well brought out by chapters by Professor Gibson on his early years in Cambridge, London, Liverpool and Oxford. Gibson also contributed a perceptive and sensitive account of Sherrington's poetry, including some hitherto unpublished items, and also a surprising list of Sherrington's gifts of mediæval books and incunabula to the British Museum, other museums and to Osler. Though many knew of his wide interest in early literature, exemplified by his monograph on Jean Fernel, the extent of these gifts is particularly remarkable in a professor of quite limited means. He was not just a collector, and his library was relatively small. Lapique has commented on his 'profound erudition'. Sherrington himself speaks of his 'favourite edition' of Descartes' *De Homine*, and in another place of reading Aristotle's *De Anima* in the original Greek. Sir John Eccles has written of the Oxford period and of the scientific and philosophical accomplishments of later years. Various previously unpublished articles and speeches and the memoir of his son Carr make up 70 pages of appendices.

Sherrington served as Professor of Physiology in Liverpool from 1895 to 1913, and Waynflete Professor of Physiology in Oxford from 1913 to 1935. In addition he held the very demanding appointment as President of the Royal Society from 1920 to 1925. Though the first World War delayed his development of the Oxford laboratory, and the post-war problems in all branches of science presented various challenges to the Royal Society, Sherrington nevertheless achieved a remarkable resurgence of his own subject. Those fortunate few who worked as graduate students and fellows in the Oxford laboratory between 1920 and 1935 found themselves part of a most exhilarating exploration of the fundamentals of nervous function. Much of this excitement is well described by Eccles in his account of graduate research in the laboratory in the last half of this period. A detailed analysis of *Man on His Nature* takes up 47 pages emphasizing the sense of wonder and the poetic beauty of Sherrington's descriptions of the physiology of the brain. The central problem that excited Sherrington was how the relationship between a network of myriads of nerve cells and fibres, each functioning in terms of transmitting nerve impulses, could develop the properties of self-awareness, mind and memory. The possibility of some special kind of activity other than conventional nerve impulses was examined and discarded. The conclusion was that a dualism between nerve function and mind is a natural mystery, insoluble by prevailing scientific knowledge. His conclusions have been criticized because they were not expressed in the current terminology of philosophers or did not closely define mind or matter in scientific terms. A curious criticism by Granit was of Sherrington's 'religiosity'. All such criticisms overlook the fact that Lord Gifford had founded the lectures to illuminate 'Natural

Theology', a presentation of natural philosophy to an audience of clergymen, without appeal to revelation. As such it was superb. Eccles does well to develop in direct quotations from the first edition the marvellous descriptions given by Sherrington of the philosophical problem as seen by a natural scientist. Sherrington's discussion of the localization of mental function relied heavily on Lashley's discussion of 1937, concluding that centres, each concerned with a particular item of intelligent behaviour, did not exist. Behaviour was damaged only by very large lesions of brain. Eccles seems unaware that since that time neurologists have given more attention to the fractionation of awareness of self and environment resulting from parietal lobe injury. Reduction of awareness leads to impairment of memory. The reflex mechanism of the tegmentum of the midbrain, with both dorsal and ventral commissures, has been shown to provide unity of perception in the split-brain situation and offers understanding of the mechanism of visual fixation. The unity of mind is still the central mystery. The analysis of *Man on His Nature* by Eccles has led him to propose in his own Gifford lectures a speculative hypothesis that he calls a 'dualist interactionism', implying a kind of super-ego that he calls the self-conscious mind. This is not discussed in this book.

The problem seems to this neurologist reviewer to belong to a general category of biological problems exemplified by the requirement of a critical mass, such as a critical number of termites, before a highly integrated 'conceptual' activity, such as the complex architecture of nest building, can begin. The neurologist, more familiar with nervous mass effects than those who work with single nerve cells, sees in this problem, not the requirement of a separate mechanism for orchestration but a more complete collaboration of a multitude of units, much as a larger computer enables a more extensive cross-correlation. This, in fact, was already foreshadowed in Sherringtonian physiology, for isolation of a greater extent of spinal cord and medulla, without introducing separate 'centres', can enable increasingly effective scratch reflex or reflex stepping.

The chapters on the scientific contributions of Sherrington deal almost exclusively with the Oxford period (1914–1935), focusing on the final solution of the problem of the synapse to which Eccles has himself contributed so much. The reader may well wonder what led to the international recognition, honorary degrees and offers of chairs in Canadian and American universities to Sherrington by 1904, after only ten years from his commencement of physiological studies. Liddell has admirably described the painfully slow development of neurophysiology in the whole nineteenth century. The impetus provided by Sherrington was enormous. He brought order out of chaos. Whereas his investigative work prior to 1892 had been purely anatomical he then settled down to a systematic examination of the distribution of nerve roots. Early in the experiments he became aware of the interaction of effects obtained from stimulation of roots innervating antagonistic muscles. In addition to his large papers on the roots in 1892, 1894 and 1898 he published a series of short notes on these reflex interactions and on spinal shock. Thus emerged the principles of reciprocal innervation and the demonstration of inhibitory reflex effects in a series of thirteen separate 'notes'. The investigation of inhibition was greatly facilitated by his discovery of decerebrate rigidity in 1898, which provided a steady background activity for the demonstration of inhibition as well as the means of analysing proprioceptive reflexes. If in later years he seemed to deprecate the effort spent on spinal roots it must be remembered that this was part of his innate humility. Historically this was an essential part of his methodical approach to the problem and also necessary in order to demolish the erroneous dogma of Pflüger and others. The next step was the investigation of the scratch reflex, also neglected in this book. Its special rhythm, its accurate direction by the locality of stimulus and the long internuncial paths enabled him to define the organization of convergent effects on motor neurons. The principle of the final common path, now commonplace, was revolutionary in 1904. The scratch reflex is still the prototype of spinal reflex organization. With Grünbaum he had also made a detailed exploration of the effects of stimulation of cerebral cortex in higher apes. The lability and frequent reversals of cortical response led to his masterly chapter on cortical reactions and their dependence on distance receptors in the *Integrative Action of the Nervous System*. This book, dedicated to his friend David Ferrier, became required reading for generations of physiologists and neurologists and was reprinted six times by 1920. A special edition published by the Physiological Society in 1947 has also been reprinted.

The years 1906 to 1920 were also much more fruitful than this book implies. In this period there was a detailed analysis of postural and stepping reactions, swallowing, pinna reflexes and further analysis of reflex inhibition. In 1925 came the definitive statement of the characteristics of synaptic excitation and inhibition in the mammalian spinal cord, culminating thirty years of experimentation. Sherrington disappeared for two weeks and came back with the manuscript. Eccles makes the extraordinary statement that 'This frankly speculative paper was not received enthusiastically. Most scientists erroneously believe that science should be concerned only with the experimentally discovered facts' (p. 61). A pharmacologist is quoted as referring to this paper as a 'bunch of speculation'. This is emphatically erroneous. Sherrington's paper gave careful documentation by quotation of detailed findings in 39 separate research reports he had made in the preceding twenty-five years. This was an impressive array of 'experimentally discovered facts' marshalled in reply to Adrian's review of 1924 favouring electrical synaptic transmission, with Wedensky type interference of conflicting rhythms as a basis for inhibition. Loewi's paper of 1921 and that of Brinkman and van Dam of 1924 were cited by Sherrington in favour of a humoral transmitter of two opposed synaptic states E and I with a chemical or ionic basis. This certainly led to further research culminating in the demonstration of production of ACh during transmission by Dale and Feldberg (1934), the existence of small electric depolarizations and hyperpolarizations by Brock, Coombs and Eccles in 1952 and Curtis and Eccles 1959 with corresponding electron micrographic characterization of synapses by de Robertis and by Palay in 1958. The irony of the situation is that in certain non-mammalian forms electrical transmission at synapses does in fact occur (Furshpan and Potter 1959; Furukawa and Furshpan 1963). The development of Sherrington's views on the nature of synaptic transmission was, in fact, methodical and progressive, established by extensive experimentation at every step and was itself a great achievement. His earlier papers included the difficult proof that the essential process of inhibition was localized in the spinal cord, and later at the synapse. Already in 1908, in disproving the views of Haidenhain regarding inhibitory 'block', he concluded that excitation and inhibition 'may be thought of as altering oppositely the permeability of the synaptic membrane . . . or the substance of the motoneurone'. In 1913 he described the intimate nature of excitation and inhibition in a long paper with many detailed experiments, concluding that 'the two processes consist essentially of one reaction that is reversible in direction'. We therefore have little patience with the statement that the 1925 paper was 'frankly speculative', or the conclusion of Granit that it was just a 'theoretical' exercise directed to subsequent testing and development.

It is obvious that there are many other aspects of the life of Sir Charles Sherrington that merit further discussion. If we differ in regard to two or three statements we must also make it clear that this memoir is outstanding not only in publishing much new material but in its attractive design, illustrations, eminent readability and scholarship.

D. DENNY-BROWN

The Deaf School Child: Language and Cognitive Function. By R. CONRAD. 1979. Pp. 370. London: Harper and Row. Price £12·50.

This book is a masterpiece. It is the report of a single piece of research, undertaken with enormous care and effort. The work itself has immediate practical implications for the care of deaf children; but its more general and theoretical impact will be wide-ranging throughout a number of branches of psychology and medicine, and there are even some implications for science policy.

Briefly, the author and his small team have set out to locate and assess every deaf child in England and Wales who is of school leaving age and has been receiving special education. In a few cases, carefully documented, they failed. They have however seen the overwhelming majority of the children in this group, so that we have here an account not of a sample but of the whole cross-section of the population, who have this handicap and were passing the crucial age at this time. Some of them were special cases, either because their parents were not English-speaking, or because the child became deaf after the third birthday when it could already talk, or because the medical history was deficient. There remain however the results on 468 children, all of whom have become deaf before acquiring a grasp of language, who were not severely multiply handicapped, and who came from homes whose first language was English.

The performance of each child was measured on a number of standard tests. These included a measure of non-verbal intelligence, a standard test of reading ability, a measurement of the ability to lip-read, and an assessment of the intelligibility of the child's own speech, both by the rating of teachers and also by the objective accuracy of listeners trying to understand tape recordings. A special test measured the extent to which the child was memorizing by means of internal speech, by assessing the efficiency of memory for a list of words whose names sound alike, such as 'zoo, screw, true, few' and a list of words whose names sound quite different, such as 'farm, home, lane, been'.

Three major points emerged. In the first place, deaf children reach this age with a very severe level of handicap indeed. Three-quarters of them cannot read even at the level of an 11-year-old, and over a third are below the 7-year-old level; that is, they are for all practical purposes totally illiterate. Only 4 per cent can read complex materials. If one considers the speech of the child, the position is almost as black. For the 40 per cent of children with the worst deafness, judges could understand on test less than one in ten of the words they spoke; and the ratings of their own teachers corresponded quite well with this measurement. The ability to understand somebody by reading lips was reasonably high if the degree of deafness was fairly slight. For the most deaf third of the children, however, less than one child in five could reach an acceptable standard of lip-reading.

It is clear from these figures that early deafness has a devastating effect on the intellectual life of the young adult. Not merely do deaf children have a problem in understanding what somebody says; nor even in making themselves understood. They are also severely handicapped in understanding language by the printed word. All this contrasts of course with the ability of a few gifted deaf individuals to make their way in the world. These cases attract admiration and attention; but perhaps distract us from the more typical prognosis for those who are deaf in infancy. Furthermore, as the book points out, these individuals often have levels of deafness which are less severe than the average child who receives special education.

The second point made by the book is that these deficiencies are linked to the failure to establish an internal code for thinking about the world; when one holds constant intelligence, or degree of hearing loss, failures in reading, talking, or lip-reading are much less severe in children who show evidence of talking internally to themselves, as assessed by Conrad's special test.

The third point made by the book is therefore that existing methods of education, which rely on teaching the deaf child to speak, are obviously failing in a large number of cases. It would be desirable therefore to find some other kind of code in which cognitive operations could be carried on, which could be established in early infancy even with profoundly deaf children. One possibility is the use of manual sign language, which has been actively discouraged in most countries, because it can be seen as tending to isolate the deaf child from the normal community. Nevertheless it tends to be used by married couples, both of whom are deaf, when bringing up their children; the small number of children in this position turn out to be better both at reading and at lip-reading than other comparable children born to parents who had normal hearing. It is at this stage that Conrad makes one of his most acute points. When earlier investigators have examined children who had been brought up to use signs, they have found no particular advantage in their performance as compared with other children of comparable intelligence. However, Conrad shows that such children actually have higher scores on the intelligence test than deaf children matched on other factors; it is surely possible that the use of a sign language in infancy has improved the cognitive machinery of the child to such an extent that its intelligence test performance is better, and that therefore matching such children with others of the same IQ is eliminating a genuine effect. The implication, obviously, is that the education of the deaf ought to give active consideration to signing as a means of communication with the deaf infant, in the interests of improving its general intellectual performance.

Such a brief summary does little justice to the texture of the book. The dissection of the relationships between hearing loss, intelligence, internal speech, and performance on each of the tests requires obsessional detail; yet the book moves easily between such detail and the broader implications for thought processes or for educational policy. By the nature of things, measurement of what is happening now cannot by itself give a guaranteed answer to those who would like to know the effects of other possible policies. Conrad's suggestion of expansion of signing may not be the right answer, but he makes a powerful case, and beyond all doubt he has shown that the present situation is producing unsatisfactory results. Furthermore, the strong implication that one form of handicap may generate general intellectual deficits has wide-ranging theoretical implications.

Lastly, it is interesting to reflect on some of the implications of this book for science policy. This is one of the most directly relevant pieces of research which has appeared in psychology in the past decade. Yet it did not result from a committee decision about areas of priority: nor did it come from the diversion of large sums of money. On the contrary, this work came from the initiative of a determined scientist, who wanted to do it, and from the wisdom of the Medical Research Council who supported him on a small scale to do it. The beginnings of the study lie twelve years ago, when Conrad first began to devote himself to examining the problem; and it is particularly interesting that this long haul could never have been undertaken by a bright young man on a project grant or post-doctoral, anxious to bang out a few quick papers before relaxing into the permanency of a teaching position. It is no accident that Conrad is a tenured research worker, with a long history of successful achievement in other fields before he turned to this new and risky enterprise. Could it be that the right way to get research of practical value is, after all, the old Medical Research Council doctrine of finding a good man and supporting his hunches?

DONALD BROADBENT

Myotonic Dystrophy. By Peter S. Harper. 1979. Pp. 331. London: W. B. Saunders. Major Problems in Neurology—Volume 9. Price £17·25.

Perhaps more than any other disorder myotonic dystrophy offers something for everyone. The disease may present at almost any age with a bewildering array of manifestations of multi-system involvement. The muscles, the eye, the brain, the peripheral nervous system, the endocrine glands, the heart, and smooth muscle may all be involved. The differential diagnosis of partial forms of the disease is wide and, despite the dominant inheritance characteristic of the disorder, its genetic basis is complex. Adult cases tend to arise from paternal inheritance, but a severe and curiously different form of the disease is found in infants born to dystrophic mothers. These diverse manifestations offer a challenge to clinical and scientific investigation by workers in many different fields. Indeed, the literature on myotonic dystrophy is immense. There have been several monographs on the disease published in the one-hundred years since it was first recognized, but fifteen years have passed since the well-known account by Caughey and Myrianthopoulos was published. In that time there have been many new contributions to knowledge of the disease. Because of the protean nature of the disorder much of this newer information is scattered in a wide selection of specialist journals and Dr Harper has performed a timely service in bringing together so much information within the covers of a monograph. In such a complex disorder the clarity of vision of a single author is particularly welcome. The book is particularly clear on genetic aspects of myotonic dystrophy, in which the author has a special interest, but clinical, EMG, pathological and biochemical aspects are fully described. Recent studies of muscle fibre and red blood cell membrane morphology and biochemistry receive detailed attention in the final chapters of the book and it is here that recent research has been most active. More practical points, such as what advice to give a young woman with myotonia and cataract seeking information on the probability of the disease manifesting in her children, are covered in a clear and concise fashion. This book will be an invaluable companion for all those concerned in the management of myotonic dystrophy.

MICHAEL SWASH

FORTHCOMING EVENTS

The Tenth International Symposium on Cerebral Blood Flow and Metabolism will take place from June 16 to 21, 1981 at Stouffer's Riverfront Towers, St. Louis, Missouri, USA. All abstracts should be submitted by November 1, 1980.

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Brain

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Volume 103 Part IV December 1980

The Substantia Gelatinosa of the Spinal Cord: a Critical Review. F. Cervero and A. Iggo ... 717

Comparison of the Effects of Transcortical and Transcallosal Removal of Intraventricular Tumours. Gina Geffen, Anthony Walsh, Donald Simpson and Malcolm Jeeves ... 773

Paralytic Rabies: a Clinico-pathological Study. J. S. Chopra, A. K. Benerjee, J. M. K. Murthy and S. R. Pal ... 789

The Effect of Spinal Cord Stimulation on Function in Patients with Multiple Sclerosis. D. J. Read, W. B. Matthews and R. H. Higson ... 803

Paræsthesiæ from Ectopic Impulse Generation in Human Sensory Nerves. José L. Ochoa and H. Erik Torebjörk ... 835

The Clinical Course of Subdural Hæmatoma. A. R. Wintzen ... 855

A Grab Reflex in the Human Hand. M. M. Traub, J. C. Rothwell and C. D. Marsden ... 869

Transmission and Scanning Electron Microscopy of Spongiform Change in Creutzfeldt-Jakob Disease. S. M. Chou, W. N. Payne, C. J. Gibbs, Jr. and D. C. Gajdusek ... 885

Human Visual Responses in the Absence of the Geniculo-calcarine Projection. J. L. Barbur, K. H. Ruddock and Vicki A. Waterfield ... 905

The Pathogenesis of Ischæmic Neuronal Damage Along the Cerebral Arterial Boundary Zones in *Papio Anubis*. J. B. Brierley, Pamela F. Prior, Jane Calverley, S. J. Jackson and A. W. Brown ... 929

An Autoradiographic Study of Human Gliomas: Growth Kinetics of Anaplastic Astrocytoma and Glioblastoma Multiforme. T. Hoshino, J. J. Townsend, I. Muraoka and C. B. Wilson ... 967

Startle Disease or Hyperekplexia: Further Delineation of the Syndrome. Frederick Andermann, Daniel L. Keene, Eva Andermann and Luis Felipe Quesney ... 985

Notices of Recent Publications ... 999

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ERRATUM

Effects of Ageing on Local Rates of Cerebral Glucose Utilization in the Rat. C. B. Smith, C. Goochee, S. I. Rapoport and L. Sokoloff. *Brain* (1980) **103,** 351–365.

Table 6 from the above paper was printed incorrectly and the corrected version is given below. The authors regret their error.

TABLE 6. AUDITORY SYSTEM

	Local cerebral glucose utilization§ (μmol/100 g/min)		
Structure	*Young adult (5)*	*Middle-aged (7)*	*Aged (6)*
Auditory cortex (cortical area 41)	139±9	120±6	121±4
Auditory cortex, layer IV	169±8	138±7*	138±4*
Medical geniculate body	125±3	105±4*	108±5*
Inferior colliculus	184±8	149±4**	148±8**
Lateral lemniscus	112±4	100±3	86±5**
Superior olivary nucleus	133±7	115±3	106±3**
Cochlear nucleus	130±17	119±1	107±6

OLFACTORY SYSTEM

	Local cerebral glucose utilization§ (μmol/100 g/min)		
Structure	*Young adult (5)*	*Middle-aged (7)*	*Aged (6)*
Olfactory cortex (cortical area 51)	122±5	103±7	106±6

§ The values are the means ± the standard error obtained in the number of animals indicated in parentheses. * Significantly different from young adult rats; $P < 0.05$. ** Significantly different from young adult rats; $P < 0.01$.

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Volume 103 Part IV De mber 19

The Substantia Gelatinosa of the Spinal Cord: a Critical Review. F. Cervero and A. Iggo ... ...

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Paralytic Rabies: a Clinico-pathological Study. J. S. Chopra, A. K. J. M. K. Murthy and S. R. Pal ... ...

The Effect of Spinal Cord Stimulation on Function in Patients with Mult Sclerosis. D. J. Read, W. B. Matthews and R. H. Higson 3

Paræsthesiæ from Ectopic Impulse Generation in Human Sensory Nerves. José L. Ochoa and H. Erik Torebjörk 835

The Clinical Course of Subdural Hæmatoma. A. R. Wintzen 85

A Grab Reflex in the Human Hand. M. M. Traub, J. C. Rothwell and C. D. Marsden ... ...

Transmission and Scanning Electron Microscopy of Spongiform Change in Creutzfeldt-Jakob Disease. S. M. Chou, W. N. Payne, C. J. Gibbs, Jr. and D. C. Gajdusek 885

Human Visual Responses in the Absence of the Geniculo-calcarine Projection. J. L. Barbur, K. H. Ruddock and Vicki A. Waterfield 905

The Pathogenesis of Ischæmic Neuronal Damage Along the Cerebral Arterial Boundary Zones in *Papio Anubis*. J. B. Brierley, Pamela F. Prior, Jane Calverley, S. J. Jackson and A. W. Brown 929

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Startle Disease or Hyperekplexia: Further Delineation of the Syndrome. Frederick Andermann, Daniel L. Keene, Eva Andermann and Luis Felipe Quesney 985

Notices of Recent Publications 999

DYSLEXIA

DYSLEXIA

A Solution to the Riddle Dyslexia

New Concepts in Diagnosis, Prediction, Treatment and Prevention
by **Harold N. Levinson, M.D.,**
Clinical Associate Professor of Psychiatry, New York University Medical Center
1980. 95 figures. XV, 396 pages. Cloth DM 48,–; approx. US $ 28.40 ISBN 3-540-90515-4

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THE SUBSTANTIA GELATINOSA OF THE SPINAL CORD

A CRITICAL REVIEW

by F. CERVERO *and* A. IGGO

(*From the Departments of Physiology and Veterinary Physiology, University of Edinburgh, Edinburgh EH8 9AG*)

INTRODUCTION

THE ORIGINS OF THE TERM 'SUBSTANTIA GELATINOSA'

ANATOMY OF THE SUBSTANTIA GELATINOSA
- I. *Boundaries of the Substantia Gelatinosa*
- II. *The Marginal Zone*
  - *Marginal cells*
  - *Other neuronal elements in the marginal zone*
- III. *The Cells of the Substantia Gelatinosa*
  - *Central cells*
  - *Limiting cells*
  - *Is the substantia gelatinosa a 'closed system'?*
- IV. *The Tract of Lissauer and its Relations with the Substantia Gelatinosa*
- V. *Peripheral Inputs to Marginal and Substantia Gelatinosa Neurons*
- VI. *Intraspinal and Supraspinal Inputs to Marginal and Substantia Gelatinosa Neurons*
- VII. *Comparative Studies on the Substantia Gelatinosa*

PHYSIOLOGY OF THE SUBSTANTIA GELATINOSA
- I. *The Substantia Gelatinosa as a Sensory Nucleus*
  - *The substantia gelatinosa and pain*
  - *Afferent input to the spinal cord*
- II. *Physiology of the Marginal Zone*
  - *Non-specific neurons in the marginal zone*
  - *Morphology of neurons*
- III. *Physiology of Substantia Gelatinosa Neurons*
- IV. *Descending Influences on Marginal and Substantia Gelatinosa Neurons*
- V. *Histochemistry and Pharmacology of the Substantia Gelatinosa*
- VI. *Current Opinions on the Functional Role of the Substantia Gelatinosa*

CONCLUDING REMARKS

INTRODUCTION

THE current upsurge of interest on the anatomy and physiology of the substantia gelatinosa (SG) of the spinal cord has led to widely scattered publications. This review aims to draw them together and place them in perspective with older ideas. In spite of the extensive studies carried out on many aspects of spinal cord physiology, the small cells of the SG have been slow to reveal their secrets. In contrast, a great deal of information has been gathered during the past twenty years on the functional responses of the larger dorsal horn neurons and their role in sensory mechanisms. In the course of these studies the small cells of the SG resisted all attempts to record their electrical activity during many thousands of traverses by exploring microelectrodes. Breaking down their opposition became a technical challenge and a source of scientific pride. A perhaps natural consequence of the lack of direct information on the SG was the invocation of SG cells in every theoretical model of sensory organization of the spinal cord. If a group of neurons with peculiar functional attributes was needed to fill a gap in a theoretical model why not implicate the elusive SG neurons? Free, if not wild, speculation has had a seminal effect on functional studies of the SG cells. Current interest on the mechanisms of pain has also focused the attention of neurophysiologists on the SG. The termination of numerous unmyelinated afferent fibres in the SG gave rise at the beginning of the century to the suggestion that the SG was involved in pain mechanisms (Ranson, 1913, 1914*a*). This view was more recently implemented on the 'gate control theory of pain' by Melzack and Wall (1965) in which SG neurons were given a key role. These hypotheses and the extensive subsequent investigations had much to do with attempts of unveiling the secrets of the SG. It is important to note that the present interest on the SG is neither a novelty, nor are the sometimes conflicting reports resulting from current studies foreign to the history of scientific inquiry on the SG. The SG was the first region of the grey matter to be identified as a sub-nucleus (Rolando, 1824), even before motoneuronal pools in the ventral horn were described. Soon after its description as a separate entity, it was implicated in reflex activity of the spinal cord and cells were found in it to which sensory functions were attributed (Grainger 1837; van Deen 1841). Continuous anatomical studies during the nineteenth century produced a fairly complete picture of its morphological organization, although unanimity of opinion on the neural nature of the SG was only slowly reached. In contemporary times, some of the classical, and apparently well-established, views on the afferent inputs to SG cells are also being challenged.

This review aims to give a critical account of present ideas on the anatomy and physiology of the SG by reference to past and present conflicts and by outlining the historical context of contributions to the knowledge of the SG. Supplementary reading is provided by an exhaustive review of literature on sensory mechanisms of the spinal cord, including the SG, recently published by Willis and Coggeshall (1978).

THE ORIGINS OF THE TERM 'SUBSTANTIA GELATINOSA'

The original description of the SG is generally attributed to the anatomist Luigi Rolando, who in 1824 published a monograph in Italian on the anatomy of the spinal cord. The book contains detailed descriptions of the external features of the spinal cord and a general outline of its internal organization. Rolando drew attention to previously unremarked differences between the posterior grey matter (dorsal horn) and the anterior grey matter (ventral horn). Based on macroscopic observations on fresh spinal cords of oxen, pigs and sheep, he stated that the posterior third of the grey matter consists of a darker and less pink grey matter. This substance was more gelatinous ('più gelatinosa') than the rest of the grey matter. In the figure legends of his book, this part of the dorsal horn is referred to as posterior grey matter of gelatinous aspect ('sostanza cinericcia posteriore d'aspetto gelatinoso') or quasi-gelatinous posterior grey matter ('sostanza cinericcia posteriore quasi gelatinosa'). No attempt was made to give that part of the dorsal horn a distinct name nor were its limits meticulously laid down. The adjective 'gelatinous' was used to distinguish the more dorsal grey matter from the ventral 'spongy and vascular' grey matter ('sostanza cinericcia spugnosa e vascolare').

The SG entered into the scientific literature with that Latin name thanks to Remak who in 1838 published his thesis in Latin. In this book Remak also describes what are now recognized as the unmyelinated peripheral nerve fibres. When he comes to describe the spinal cord and hence Rolando's observations, Remak writes on that 'substantia gelatinosa' described by Rolando. The Latin origins of the modern Italian language and the chance of a Northern European scholar writing in Latin transformed that 'sostanza più gelatinosa' described by Rolando, into the 'substantia gelatinosa Rolandi'.

Following Rolando's observations, Remak divides the grey matter ('substantia cinerea' = ashy matter) into a dorsal substantia gelatinosa and a ventral substantia spongiosa and qualifies as of 'gelatinosa' texture other parts of the spinal cord and brain such as the 'commissura gelatinosa' (later to become the substantia gelatinosa centralis of the spinal cord) and the 'substantia gelatinosa cerebri' (localized in the hippocampus).

The use of Latin as a scientific language both in full reports or to designate anatomical structures produced in the nineteenth and early twentieth centuries several variations on the straightforward term 'substantia gelatinosa'. Among them are: 'substantia Rolandi' (Owsjannikow, 1854); 'substantia gelatinosa (Rolando)' (Stilling, 1859*a*, *b;* Kölliker, 1860); 'formatio Rolandica'. (Lenhossék, 1895); 'substantia gelatinosa Rolandoi' (Marburg, 1904) and 'substantia Rolandica' (Waldeyer, 1888). The official nomenclature established by the Nomina Anatomica christened the SG as 'substantia gelatinosa (Rolandi)' in 1895 (Basle Nomina Anatomica); 'substantia gelatinosa dorsalis' in 1935 (Jena Nomina Anatomica) and 'substantia gelatinosa' in all editions since Paris (1955, 1961, 1966, 1977).

ANATOMY OF THE SUBSTANTIA GELATINOSA

I. *Boundaries of the Substantia Gelatinosa*

Early studies on the anatomy of the spinal cord showed that the SG is present throughout its whole length (Stilling, 1859*a*, *b*) and extends into the medulla oblongata, where it forms the SG of the trigeminal nucleus (Stilling, 1846). In fact the SG is the only structure of the spinal cord extending continuously from the brain-stem to the filum terminale (Bruce, 1901; Jacobsohn, 1908; Sano, 1909; Kappers, Huber and Crosby, 1936).

The total dorso-ventral extension of the SG and the recognition of layers within it have been and remain controversial issues. Rolando (1824) described the SG as the most posterior third of the grey matter thus including in it a significant part of the dorsal horn. His description was based on the observation of the fresh, unstained cords and in the obvious differences in colour and consistency between the superficial dorsal horn and the rest of the grey matter. In one figure Rolando depicts the border between the SG and the 'vascular' matter as a wavy line and states in the legend that this boundary resembles the sutures of the cranial bones. A very recent paper (Light and Perl, 1979*a*) has emphasized this unevenness along the border between the SG and the rest of the dorsal horn.

The statement by Rolando that the SG forms the posterior third of the grey matter led some authors to the belief that most of the dorsal horn was formed of gelatinous substance (van Deen, 1841). It is, however, very clear from his figures that Rolando assigned much less space to his gelatinous substance than the whole posterior third of the grey matter. Stilling (1859*a*) and Clarke (1859) described the limits of the SG in detail. Both authors agree that the SG forms only a comparatively narrow and curved lamia or band around the extremity of each dorsal horn. Clarke (1859) added that when viewed in a thin transverse section of the cord the SG appears much paler and more transparent than the rest of the grey matter. Stilling and Clarke were involved in a virulent personal polemic reflected in their papers by angry and deprecatory comments on each other's work as well as claims of priority on the description of many spinal cord features. It is therefore very difficult to know exactly the order of their discoveries but it seems clear that both authors recognized the presence of different kinds of cells in the SG and divided this area into two zones: an outer region containing large and spindle-shaped cells and a larger inner region packed with very small cellular elements. Clarke (1859) in particular divided the head of the dorsal horn (caput cornu) into an outer portion or gelatinous substance and an inner portion with cells of intermediate size and rich in longitudinal fibres. He also stated that the SG had a 'stratum of large cells and marginal nerve-fibres along its posterior border next (to) the posterior column, into which some of the processes of the cells may seen to extend'.

The recognition of the superficial SG as an independent layer was the work of Lissauer (1886) and Waldeyer (1888). Following traditional nomenclature, Lissauer (1886) considered two substances in the grey matter of the spinal cord: substantia gelatinosa and substantia spongiosa. He stated that the substantia gelatinosa, located in the superficial dorsal horn was covered on its dorsal aspect by a fine layer of substantia spongiosa similar to the rest of the grey matter and called it 'Spongiõse Zone der gelatinõsen Substanz'. The term 'zona spongiosa' is still present in anatomical dictionaries (Donath, 1969) meaning 'a layer on the dorsal aspect of the SG of the spinal cord which contains elongated fusiform cells'. In the same article Lissauer described the propriospinal tract in the apex of the dorsal horn that bears his name. Waldeyer (1888) paid more attention to the superficial dorsal horn. He described in detail the large and flat cells on the posterior border of the SG as an independent layer, called it the 'peripheral zonal layer' (die periphere Zonalschicht) and its cells 'marginal cells' (marginale Zellen, marginale Hinterhornzellen).

This area was later named 'Zona marginal de Waldeyer' by Ramón y Cajal (1899), 'stratum zonale' by Ziehen (1899); 'nucleus magnocellularis pericornualis' by Jacobsohn (1908) and 'gruppi pericornuali del cordone laterale' by Massazza (1922-1924). Other authors referred to it as the 'zone of Waldeyer or Lissauer' (Kappers *et al.*, 1936) which, although paying tribute to both discoverers created much confusion since the propriospinal tract of the apex of the dorsal horn was also called Lissauer's tract. Even the thorough historical review of Rexed (1952) on the anatomy and histology of the dorsal horn contains some bibliographic errors due to his mistaken interpretation of Lissauer's zone and Lissauer's tract. Similarly, Lissauer's tract is called Lissauer's marginal zone in the series of phylogenetic studies of the SG by Keenan (1928, 1929*a*,*b*).

Ranson (1913, 1914*a*) divided the SG into two layers (the zonal layer and the SG proper) and distinguished a third layer of fibres and transitional cells just ventral to the SG which formed an intermediate layer between the SG and the nucleus of the dorsal horn. This transitional layer which is well depicted in the excellent figures of Stilling (1859*b*) and Clarke (1859) had been recognized before by Rosenzweig (1905) as the 'Greuzschicht'; by Kölliker (1860) as 'Plexus der Substantia Gelatinosa' and by Ziehen (1899) as the 'dorsalen Greuzplexus des Hinterhornkopfs'.

In summary, by the end of the 1930s scientific opinion regarding the extent and stratification of the SG was as follows: the SG was defined as the most superficial part of the dorsal horn, distinguishable from the rest of the grey matter by its peculiar consistency and transparency. Some authors (Clarke, 1859; Stilling, 1859*a*; Lenhossék, 1895; Ramón y Cajal, 1899, 1909; Ziehen, 1899; van Gehuchten, 1900 and Ranson 1913) divided it into the narrow marginal zone containing larger neurons and the SG proper with smaller cellular elements. Other anatomists (Lissauer, 1886; Waldeyer, 1888; Marburg, 1904; Jacobsohn, 1908; Massazza, 1922-1924, and Kappers *et al.*, 1936) considered the marginal zone to be a separate layer of the grey matter. In addition, a special transitional region just ventral to the SG proper had been recognized (Stilling, 1859*a*; Clarke, 1859; Kölliker, 1860; Ziehen, 1899; Rosenzweig, 1905; Ranson, 1913).

It is in this context that Rexed's cytoarchitectonic studies on the spinal cord (1952, 1954) must be analysed. He described the grey matter of the spinal cord as being built up of a number of cell layers in a manner similar to the cerebral cortex or the thalamus and strongly emphasized the cytoarchitectonic basis of his studies. The grey matter of the spinal cord was divided into nine cell layers, named laminæ I-IX. The first three were identified with the marginal zone of Waldeyer (lamina I), the substantia gelatinosa Rolandi (lamina II) and the dorsal part of the nucleus proprius (lamina III). Lamina IV corresponded to the ventral part of the nucleus proprius (making with lamina III the 'head of the dorsal horn' of older literature) and laminæ V and VI were identified with the 'neck of the dorsal horn' of Clarke (1859).

Rexed (1952) described lamina I as a 'thin veil of grey substance forming the most dorsal part of the spinal grey matter'. The main cellular feature of this lamina was the presence of the large marginal cells intermingled with small and medium-sized cells. Lamina II (the SG, according to Rexed) was a 'well-delineated band' across the dorsal horn and consisted of 'tightly packed, small cells'. Rexed distinguished two zones in lamina II: a dorsal or outer zone which contained the smallest cells and a ventral or inner zone which appeared as a 'lighter, less compact part of the lamina II'. Finally, lamina III formed a band, parallel with laminæ I and II containing larger nerve cells than lamina II and less closely packed.

This description by Rexed (1952), based purely on cytoarchitectonic grounds, initiated a polemic that has not yet been resolved. The debate is on whether the SG of earlier literature corresponds only to lamina II, as Rexed had described or to both laminæ II and III together. An interesting consequence of Rexed's work was also the emergence of the marginal zone as a separate independent layer (lamina I) and the consignment to limbo of earlier interpretations of the marginal zone as the superficial layer of the SG (Ranson, 1914*a*).

A central issue of the polemic on the correspondence between Rexed's laminæ and the SG is whether the cells of lamina II can be separated from the cells of lamina III on morphological and/or functional grounds. In the discussion that followed the presentation by Rexed in 1964 of his laminar scheme the morphological (Szentágothai) and physiological (Wall) identity between laminæ II and III were suggested. Rexed insisted on the distinction between these two laminæ based not only on a difference in cell size but also on the higher fibre content of lamina III and the presence of a well-defined borderline between the SG (lamina II) and the dorsal aspect of the nucleus proprius (lamina III). Rexed also insisted on the difficulties of relating Golgi studies to cytoarchitectonic analysis. Szentágothai (1964), using Golgi methods, had concluded that, in spite of the somewhat larger size of the cells in lamina III, the general anatomical features of the neurons in laminæ II and III and 'especially their connections' were identical. He thus equated these laminæ to the SG of earlier literature. Wall (1962, 1965) agreed with this view on the basis of source-sink analysis of field potentials in the dorsal horn (Howland, Lettvin, McCulloch, Pitts and Wall, 1955). They were unable to find differences across the area corresponding to Rexed's laminæ II and III. In a recent single-unit study of the SG, Wall, Merrill and Yaksh, (1979) continue to treat laminæ II and III as a functional and morphological unit corresponding to the SG.

The larger size of the neurons in lamina III and the lower cellular density of this area are not the only reasons for distinguishing it from lamina II. Ralston (1965) noted that lamina II did not take osmium when specimens were prepared for electron microscopy, due to the paucity of myelinated afferent fibres. He excluded lamina III from the SG in view of its differences in afferent input with lamina II (Ralston, 1965). The lack of myelinated afferent input to lamina II does not imply that the neurons of this area were not connected to dorsal root afferents. The conflicting reports on the effects of dorsal rhizotomy on degeneration of afferent terminals in the dorsal horn were resolved by Heimer and Wall (1968) who showed a difference in degeneration time of the dorsal root terminals in lamina II as opposed to lamina III. Furthermore, Ralston (1968*b*) found numerous terminals from unmyelinated dorsal root afferents in lamina II, thus adding support to the identification of this lamina with the classic SG. Scheibel and Scheibel (1968) attempted a compromise solution by proposing the name 'gelatinosal complex' for laminæ II and III, thereby subsuming some similarities but not total identity between the two laminæ. This view has been followed by Beal and Cooper (1978). Histochemical studies showed a differential distribution of acid phosphatase in the superficial dorsal horn. It was present in terminals of presumed unmyelinated dorsal root afferents that ended exclusively in lamina II (Coimbra, Magalhaes and Sodre-Borges, 1970; Knyihar, 1971), which led Coimbra, Sodre-Borges and Magalhaes (1974) to identify lamina II with the classic SG.

The evidence indicating a differential distribution of dorsal root afferents in the superficial laminæ of the dorsal horn has, more recently, received a great deal of support. Electron microscopy (Ralston, 1965, 1968*b*; Beal and Cooper, 1976) and Golgi studies (Beal and Fox, 1976; Réthelyi, 1977) have revealed numerous myelinated fibres in lamina III in contrast to a small number in lamina II, as well as an almost exclusive distribution of unmyelinated afferents in lamina II. Based on these and further observations of the same nature Ralston (1979) has followed Rexed's original division of the SG (lamina II) into two layers; an outer lamina II with smaller cells and only unmyelinated terminals and an inner lamina II with both unmyelinated and small myelinated endings (Ralston, 1979; Ralston and Ralston, 1979). A somewhat different division, with the inner SG extending into part of lamina III had been proposed earlier by Beal and Cooper (1978).

Intracellular staining with horseradish peroxidase (HRP) of individual dorsal root afferents and dorsal horn neurons has added a new dimension to the debate. Neither the dendrites of some large neurons in lamina IV nor the endings of thick myelinated dorsal root afferents penetrate lamina II (Brown, House, Rose and Snow, 1976; Brown, Rose and Snow, 1977*a*, *b*). All these structures are, however, present in large numbers in lamina III. On the other hand, small myelinated afferents end in lamina I, the ventral side of lamina II and the whole of lamina III (Light and Perl, 1979*a*, *b*), whereas unmyelinated fibres seem to end only in lamina II. The concept of a morphological and functional identity of laminæ II and III no longer appears to be tenable.

On the basis of past and present descriptions of morphological features of the SG the following conclusion on the boundaries of this region can be reached: The substantia gelatinosa is a band of clearer grey matter located in the dorsal-most part of the dorsal horn; it contains small neurons and terminals of dorsal root unmyelinated afferents in its dorsal region (outer SG) and small neurons and terminals of both unmyelinated and small myelinated dorsal root afferents in its ventral region (inner SG); ventral to the SG there is a transitional zone containing slightly larger neurons, dorsal dendrites of deeper neurons and terminals of large and small myelinated dorsal root afferents; the cell density is higher in the outer SG and decreases towards the inner SG and transitional zone; dorsal to the SG there is a thin layer characterized by the presence of large flat neurons and horizontal nerve fibres lying between the SG and the white matter. Current names of unequivocal meaning used to designate these areas are substantia gelatinosa or lamina II; marginal zone or lamina I (for the layer dorsal to the SG) and dorsal nucleus proprius or lamina III (for the layer ventral to the SG (*see* fig. 1 for anatomical details).

II. *The Marginal Zone*

The differences in fibre orientation and cell composition between the most superficial parts of the SG and the rest of this structure were noticed by Clarke (1859) and Stilling (1859*a*), both of whom state that the dorsal border of the SG was composed of a plexus of fibres running in a medio-lateral direction, perpendicular to the main axis of orientation of the rest of the fibres in the SG. Among the superficial fibres, large fusiform cells were found (Clarke, 1859; Stilling, 1859*b*). Lissauer (1886) and Waldeyer (1888) separated this layer from the SG and described it as a thin band of grey matter encircling the SG and joining with the rest of the dorsal horn through its lateral curvature. The identification of the marginal zone with the rest of the grey matter of the dorsal horn and its independence from the SG are evident in Waldeyer's descriptions and illustrations. Nevertheless, this opinion was not unanimous and recent morphological and physiological studies have shown a close relation between the SG and the marginal zone. A mention of the main features of this superficial layer seems therefore appropriate within the context of the present review. The marginal zone will be separated from the SG and the names 'marginal zone', 'stratum zonale' and lamina I will be employed as synonyms. 'Stratum zonale' is a literal latin translation of Waldeyer's original term 'Zonalschicht'. It means 'a layer that surrounds like a ring or a belt' and is therefore a very appropriate term to designate the marginal zone. 'Stratum zonale' was used by Ziehen (1899). The main neuronal elements of the marginal zone are the marginal cells. A dense plexus of horizontally running fibres and other neuronal types are also important features of this layer.

Marginal cells. Waldeyer (1888) in describing this cell type in the spinal cord of the gorilla and man, considered them as a sub-group of the cell population of the dorsal horn (marginale Hinterhornzellen) streaming out from the base of the dorsal horn and flattened between the SG and the overlying white matter. In detailed studies, using Golgi preparations Lenhossék (1895) described them as spindle- or pyramidal-shaped, with dendrites spreading out in a medio-lateral orientation and occasionally giving off branches which entered the SG. Ramón y Cajal, also using Golgi preparations, called them 'Células fusiformes marginales' (1890), 'Células fusiformes limitantes' (1891) and 'células marginales' (1899, 1909). The fact that Ramón y Cajal called the marginal cells 'limiting cells' in some of his publications is a source of confusion. He had also called 'limiting' some transitional and superficial cell types of the SG. In consequence it is not quite clear which cells he is referring to when describing or illustrating 'limiting' cells. In his view, marginal cells were displaced elements from the centre of the dorsal horn, pushed aside by the growth of the SG. Marginal cells which have also been called 'pericornual cells' (Massazza, 1922–24; Pearson, 1952), are scarce and irregularly distributed. Massazza (1922–24) distinguished three groupings of marginal cells (apical, reticular and medial groups) of which the apical group contained the greatest number of cells, particularly in lumbo-sacral segments of the cord. Several authors have pointed out that marginal cells tend to be found in widely spaced clusters (for example, Carstens and Trevino, 1978). Marginal cells have a spindle-shaped soma of moderate to large size (estimates range from 20 to 60 μm), with dendritic systems that are usually long, following the contours of the SG and occasionally penetrate it (fig. 1) (Lenhossék, 1895; Ramón y Cajal, 1899, 1909; Earle, 1952; Ralston, 1965, 1968*a*, 1979; Scheibel and Scheibel, 1968; Kerr, 1975; Narotzky and Kerr, 1978). Dendrites are few in number, infrequently branched and, with the exception of the branches that penetrate the SG, not very rich in spines. Sometimes marginal cells are found in the white matter dorsal to the superficial dorsal horn. The typical dendritic domain of the marginal cells is discoid and flattened along the dorsal border of the SG (Scheibel and Scheibel, 1968). Exact measurements of the total dendritic extension have not been produced but, based on published illustrations, it seems that marginal cells cover a circle of 1 to 2 mm diameter.

Marginal cells have thin axons that often take origin from a major dendrite, sometimes far away from the soma (Ramón y Cajal, 1899, 1909). These axons follow a course, initially tortuous, through the marginal zone and the SG dropping off a few collaterals before joining the propriospinal systems of the dorsal horn (Lissauer's tract or the dorsal fasciculus proprius). According to Szentágothai (1964) most axons of marginal cells run in Lissauer's tract for up to 5 or 6 segments before re-entering the dorsal grey matter. This view is in agreement with earlier considerations of marginal cells as propriospinal interneurons (Bok, 1928; Pearson, 1952), a view that was upheld by the Scheibels (1968) and recently substantiated by Burton and Loevy (1976) who have shown that some marginal cells have propriospinal descending axons. On the other hand, long ascending projections of marginal cells were first proposed by Kuru (1949), who found retrograde chromatolytic reactions in marginal cells in human patients after antero-lateral chordotomy. He thus suggested that marginal cells gave rise to axons projecting through the spinothalamic tract. The introduction of the method of retrograde labelling of neurons with HRP has extended the debate on the long ascending axonal projections from marginal cells. So far, marginal cells have been described projecting to the contralateral and ipsilateral thalamus in cats, monkeys and rats (Trevino and Carstens, 1975; Carstens and Trevino, 1978; Giesler, Menetrey and Basbaum, 1979; Willis, Kenshalo and Leonard, 1979), to the ipsilateral cervical nucleus in cats and dogs (Craig, 1978) and to the cerebellum in monkeys and cats but not in rats (Snyder, Faull and Mehler, 1978).

Narotzky and Kerr (1978) have suggested that there are two types of marginal cell, similar in their anatomical features but with different axonal projections. They proposed to name one group P-marginal cells (projection) and the other A-marginal cells (associational). This division recognizes the heterogeneous anatomical evidence and accounts for the existence of long and short projecting neurons within the general population of marginal cells.

Other neuronal elements in the marginal zone. Marginal cells are not the only neuronal elements in the marginal zone. One conspicuous feature which contributed to its independence from the SG in earlier descriptions was the presence of a horizontal plexus of nerve fibres. This is made up of fine dorsal root afferents, processes of marginal and other superficial neurons and axons of deeper dorsal horn neurons passing through on their way to join the dorso-lateral funiculus. The marginal cells are enmeshed in this plexus and two other classes of neurons (Rexed, 1952; Ralston, 1968*a*). The latter neurons have always been described in Nissl preparations which makes their identification with other neuronal elements of nearby regions very difficult. It is probable that the smallest cells described in the marginal zone are dorsally located SG neurons, and that the medium sized cells correspond to the 'limiting cells' of the SG described by Ramón y Cajal (1890, 1899, 1909). Both cell types are described in more detail in the following paragraphs. The division of marginal cells into long and short projecting neurons does not take into account the existence in the marginal zone of these other neurons. The neurons having locally distributed or intersegmental axons may not be typical marginal cells but some of the other cells, particularly the 'limiting' type of neuron.

III. *The Cells of the Substantia Gelatinosa*

Cellular elements in the SG were seen by Remak (1838) who described them as very small, round or oval corpuscles with nuclei; rather like red cells. Stilling (1846) strongly advocated this description, calling them 'corpora nervea globosa sine processibus' whereas Clarke (1859) gave a somewhat more accurate picture. He described two types of cells in the SG: a small, round or oval cell with a few processes and orientated in the dorso-ventral axis and a slightly larger cell type with a fusiform soma located near the border with the dorsal columns. Still more detailed and accurate descriptions were given by Gierke (1886) and Virchow (1887) and these were followed by extensive studies by Corning (1888), Lenhossék (1889, 1895), Ramón y Cajal (1890, 1891, 1899, 1909) and Golgi (1894). During this time SG cells were often called Gierke's or Virchow's cells (*see* Marburg, 1904). Ramón y Cajal studied the SG in mammals and birds and divided the cells of the SG into two main classes: (i) central cells: ('Corpúsculos centrales' (1899), 'Cellules centrales' (1909)) which are very small cells, distributed all over the SG and with a distinct longitudinal orientation, and (ii) limiting cells: ('Corpúsculos fronterizos' (1899), 'Cellules limitrophes' (1909)) that were slightly larger cells, located mainly in the superficial SG and with a horizontal orientation.

Cajal's classification has survived almost unscathed. His two classes of SG neuron have been recognized in more recent times (Pearson, 1952; Scheibel and Scheibel, 1968; Sugiura, 1975) and his descriptions have been largely substantiated. A more complex classification of morphological types in the SG, and an intricate neuronal network derived from it, has been proposed by Gobel (1975, 1978), who studied the SG of the trigeminal nucleus caudalis (which he defines as the 'dorsal horn of the medulla'). He described up to three classes of neuron: islet cells, stalked cells and spiny cells. The rather broad over-simplification which identifies the trigeminal nucleus caudalis with the dorsal horn of the spinal cord might have encouraged

Gobel to consider that the structure of the trigeminal SG ought to be in all respects similar to that of the spinal cord SG. Careful Golgi studies of the SG of the spinal cord (*see* Beal and Cooper, 1978) show that the nerve cells of this area represent a spectrum of sizes and shapes ranging from fusiform-shaped cells in the centre to the polygonal forms in the superficial SG. Cajal's original classification still stands as a useful practical simplification, although one must bear in mind that his two cell types may well represent the extremes of a spectrum of transitional forms.

Central cells. Ramón y Cajal (1890) described these cells in the cord of new-born dogs and cats and later extended his observations to chicken embryos and pigeons (Ramón y Cajal, 1891). The term 'central' cells seems inappropriate since these neurons are distributed all over the SG and not just in the centre. However, Cajal used the word 'central' to differentiate them from the 'limiting' cells which are usually located in the margins or borders of the SG. For lack of a better proposal, and in recognition of Cajal's major contribution, the term 'central cells' will be used in this paper.

Central cells have the smallest cell bodies in the whole cell population of the spinal cord (estimates range from 7 to 14μm) with large nuclei surrounded by a little cytoplasm (fig. 1) (Szentágothai, 1964; Ralston, 1965, 1968*a*; Réthelyi and Szentágothai, 1969; Coimbra *et al.*, 1974). The somata are spindle-shaped, with two profuse dendritic trees emerging from opposite poles of the cell body. The dendritic trees are extremely dense due to the multitude of branches and the numerous stalked appendages (Beal and Cooper, 1978). An important feature of the central cells is their plane of orientation in the spinal cord (Ramón y Cajal, 1899, 1909; Earle, 1952; Szentágothai, 1964; Scheibel and Scheibel, 1968; Sugiura, 1975). In the dorso-ventral direction they generally adopt a radial orientation, perpendicular to the slightly curved border of the SG. Bundles of nerve fibres run in a dorso-lateral direction between SG cells, thus giving to this area its characteristic lobular appearance. The total dorso-ventral dendritic extent is estimated at 150 to 200μm, thus covering the full SG. The mediolateral extent of individual cells is much smaller: not more than 50 to 100μm (Sugiura, 1975; Light, Trevino and Perl, 1979). In the rostro-caudal axis, in contrast, they stretch over long distances of up to nearly 2mm (Light *et al.*, 1979). This peculiar orientation of their dendritic trees gives the SG neurons of the 'central' type a nearly two-dimensional lamina format along the main rostro-caudal axis of the cord.

The axons of the 'central cells' are generally described as very thin (although Beal and Cooper (1978) give figures of up to 2 μm in diameter) and usually take origin from a primary or secondary dendrite, sometimes far from the cell body. They follow a tortuous course through the SG, dropping off several profusely branched collaterals rich in 'en passant' boutons. All axon collaterals and some main axons seem to end within the boundaries of the superficial dorsal horn (laminæ I to III) but most axons eventually reach one of several propriospinal bundles of the dorsal horn. According to Lenhossék (1895) most join Lissauer's tract. Ramón y Cajal (1899, 1909) stated that most projected to the lateral fasciculus proprius, fewer to

Lissauer's tract and a handful to the dorsal columns. On joining these paths the axons either bend and ascend or bifurcate and give ascending and descending branches. The projections through Lissauer's tract and the lateral fasciculus proprius have been substantiated by Szentágothai (1964), Scheibel and Scheibel (1968) and Sugiura (1975).

Limiting cells. These cells were first recognized by Ramón y Cajal in 1890 and described in the Spanish edition of his classic book (1899) as 'Corpúsculos fronterizos'. In the better known French translation of this book they are termed 'Cellules limitrophes'. The introduction of the adjective 'limitrophes' has created a terminological confusion, outlined by Willis and Coggeshall (1978). Ramón y Cajal had called the larger marginal cells 'Células limitantes' in his paper of 1891 and in the Spanish edition of his book of 1899. In the latter, marginal cells are called 'Células limitantes' in both the text and in the figures. The French version (1909) translated 'Células limitantes' as 'Cellules marginales' in one instance and 'Cellules limitrophes' in another, thus confusing the marginal cells of lamina I with the limiting cells of the SG. It is therefore expedient (albeit regrettable) to abandon the former Spanish or French terminology and refer to these cells as 'limiting cells'.

Limiting cells are slightly larger than central cells (about 10 to 15 μm cell body diameter) and are preferentially located in the marginal zone or in the outer SG. The main feature of the limiting cells is the appearance of their dendritic trees; a group of dendrites taking origin from the ventral side of the soma and running in a dorso-ventral direction in the SG, and another dendritic system originating dorsally and distributed over the marginal zone in a medio-lateral and rostro-caudal orientation (fig. 1). They look therefore like intermediate elements between the 'central' SG neurones and the marginal cells of lamina I. This was the opinion of Scheibel and Scheibel (1968) who described them as 'transitional' elements. Limiting cells appear to be similar to the 'stalked' cell described by Gobel (1975, 1978) in the SG of the trigeminal nucleus caudalis and have been so named by Bennett, Hayashi, Abdelmoumene and Dubner (1979) who succeeded in staining some limiting cells intracellularly in the spinal cord.

The dendritic extent of the limiting cells is different from that of the central cells. Limiting cells have a wider medio-lateral distribution (150 μm or more) and shorter rostro-caudal (400 μm) and dorso-ventral (75–150 μm) distributions. They thus correspond to the polygonal-sized neurons of Beal and Cooper (1978) and represent the extreme end of their spectrum of shapes.

The axons of limiting cells seem to have an initial course, collateral distribution and paths of projection similar to those of central cells. These thus share some morphological properties with 'central' SG neurons but differ from them in their location and the distribution of their dorsal dendrites which resembles that of marginal cells. It is, therefore, appropriate to consider them as a separate group of cells with distinct morphological features. They could also be the frequently described neurons in the marginal zone or outer SG with short projecting axons–the so-called associational marginal cells (Narotzky and Kerr, 1978).

Is the substantia gelatinosa a 'closed system'? The concept of the SG as a 'cellular system closed in itself' was put forward by Szentágothai (1964) and has remained one of the most quoted attributes of the SG as well as the basis of all morphological and functional models involving its neurons. Szentágothai was impressed by the large numbers of very small SG neurons with thin axons that apparently ended only within the limits of the SG. The only estimate of the cell density of the SG is that of Scheibel and Scheibel (1968). They give a figure of 250 to 300 cells per 10^6 μ^3 in mid-lamina II of the adult cat. From that figure it can be worked out that there are between 75 000 and 90 000 SG cells per mm of spinal cord on each side. Szentágothai described two systems of axonal projection: (i) a short range intrinsic system formed by axons of SG neurons that extend for not more than 2 to 3 mm through the SG itself and (ii) a 'long-range' system formed by those SG neurons whose axons joined Lissauer's tract or the lateral fasciculus proprius and reflected back to the SG after travelling 2 to 3 segments in either direction. A few SG neurons whose axons crossed to the other side of the cord were also proposed to end within the limits of the contralateral SG. Therefore, Szentágothai (1964) proposed that the SG was 'a cellular system almost closed in itself with a strong input from the dorsal roots and very rich interconnections longitudinally but practically no direct pathways for further forward conduction'. In view of this, Szentágothai then proposed that the only system of forward conduction from the SG would be through connections with the large neurons of laminæ IV and V, whose dendrites 'are embedded in it'. It seems well established now that dendrites of some neurons in laminæ IV and V do not enter the SG (lamina II) although they are plentiful in the dorsal nucleus proprius (lamina III) (Brown *et al.*, 1976, 1977*a*). It must be remembered that Szentágothai in his 1964 paper considered laminæ II and III together as the SG. On the one hand this substantiates his assertion that dendrites of laminæ IV and V neurons can reach the axons of SG neurons but on the other hand does not make the SG (lamina II) a closed system since the axons of its neurons could end outside it, namely, in lamina III. This may seem a rather strained argument but it is important to realise that the idea of the SG as a 'closed system' has been taken literally by many authors, implicating a great deal of intra-SG activity and very little direct interaction with neurons in other areas of the dorsal horn. Axons of SG neurons almost certainly end on other SG neurons but, in branching in lamina III, they also make contacts with neurons in this deeper lamina some of which are neurons that project through ascending pathways. Also, axonal endings from SG neurons have been described on the dendrites and somata of marginal cells, some at least of which project to supraspinal structures. Neurons in the SG are not only involved as interneurons in sensory transmission or reflex pathways. Some of them have long ascending axons. Two research groups have reported typical central and limiting SG neurons filled with HRP following its injection into supraspinal structures. Giesler, Cannon, Urca and Liebeskind (1978) described them after injecting the cervical cord and lower brain-stem in the rat, and Willis *et al.* (1978, 1979) reported retrograde transport of HRP to some SG neurons in monkeys after making injections in the contralateral thalamus.

These results call in question the concept of the SG as a 'closed system' which can only be sustained on the basis that SG neurons are largely propriospinal interneurons with axonal projections limited to the superficial dorsal horn. They are influenced by incoming activity from dorsal root afferents and in their turn they influence neurons of their own kind, larger neurons in the same or neighbouring segments, and in some instances, may project to distant segments of the cord or to supraspinal structures.

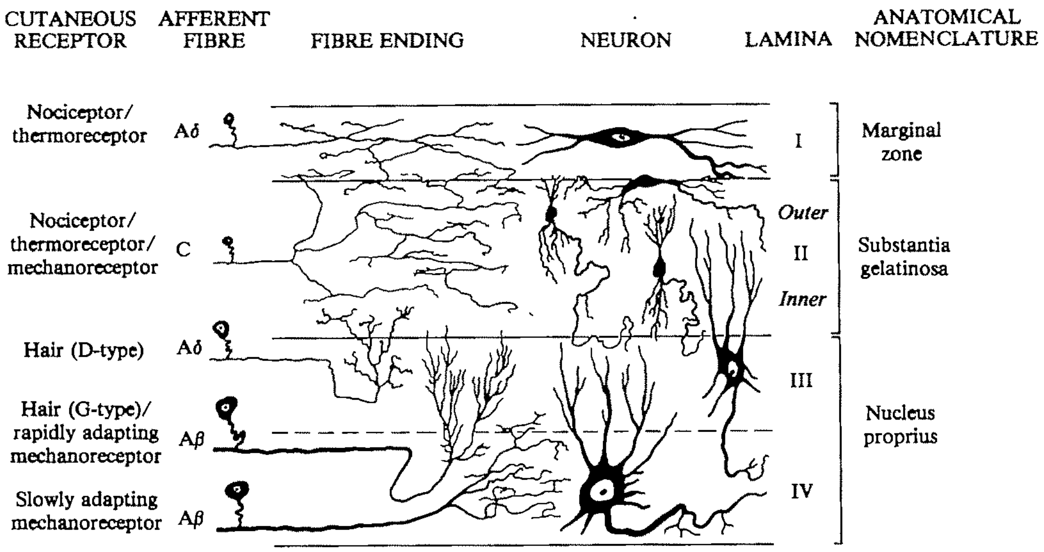

FIG. 1. Schematic diagram of the neuronal organization of, and afferent input to the superficial dorsal horn. The diagram represents an imaginary transverse section of the dorsal horn and illustrates the afferent fibre endings and neuronal elements present in the first four laminae of the dorsal horn. To the left of the diagram the types of afferent fibre and relevant receptor groups associated to them are listed. Fibre endings in the dorsal horn are schematized diagrams taken from published morphological studies. Neurons in the diagram represent standard types of neuron in the superficial dorsal horn. The following types have been illustrated: *(from top to bottom)* a marginal cell, an SG limiting cell, two SG central cells and two neurons of the nucleus proprius, the most superficial of which has dendrites penetrating lamina II. Indicated at the right of the diagram are the laminar division of the superficial dorsal horn and corresponding anatomical nomenclature.

IV. *The Tract of Lissauer and its Relations with the Substantia Gelatinosa*

The tract of Lissauer has already been mentioned as a projection pathway for the axons of some marginal and SG neurons. It also contains bundles of small myelinated and unmyelinated dorsal root afferents whose final destination is the superficial dorsal horn, particularly the marginal zone and the SG. Lissauer's tract is therefore a pathway closely associated with the SG as it groups in one distinct propriospinal tract most of the peripheral inputs to SG neurons and many of their axonal projections. The relation of the SG with Lissauer's tract has not, however, escaped its share of controversy and conflicting evidence. Three principal issues have for years been the subject of disputation and it is only very recently that definite experimental evidence has begun to emerge on (i) the nature of the fibres running in Lissauer's tract (intrinsic axons or dorsal root afferents); (ii) the axonal spectrum of the tract and (iii) the longitudinal span of the fibres in the tract. Each issue requires detailed consideration.

A small bundle of fibres, situated in the apex of the dorsal horn, between the SG and the external border of the spinal cord was described with precision by Lissauer. Preliminary observations were published in abstract form (Lissauer, 1885), and a full and excellent paper appeared one year later (Lissauer, 1886). He described fine fibres of the dorsal root that separate themselves from the coarse fibres and enter the spinal cord slightly lateral to the rest of the dorsal root fibres. On entering the cord, these fine fibres group into a bundle that runs in the border area ('Randzone') between the grey matter and the periphery of the spinal cord. To Lissauer, the tract was made exclusively of fine dorsal root afferents. The interesting observation of a segregation of fine fibres within the dorsal roots into a lateral bundle generated contradictory re-examinations. Ranson (1913, 1914*a*, *b*) confirmed the medio-lateral division of the dorsal roots and concluded that small myelinated and unmyelinated dorsal root fibres emerged into a lateral bundle that was continuous with Lissauer's tract. This was the morphological basis for his view of the SG-Lissauer's tract complex as the first relay of the pain pathway (Ranson and Billingsley, 1916). Segregation of fine afferents into a lateral division of the dorsal root was confirmed by Earle (1952) and Szentágothai (1964) although both agreed that the division was not quite as simple as Ranson had described it. Wall (1962), on the other hand, could find no evidence for a lateral division of the fine dorsal root afferent fibres. It is important to note that he considered Lissauer's tract as 'a propriospinal tract for the substantia gelatinosa' with few, if any, dorsal root fibres in it, and that the 'entering roots and Lissauer's tract are separate structures with almost no intermingling'. A recent anatomical re-examination of the area by Snyder (1977) in cats and monkeys has shown that there is a lateral division of the dorsal root containing small myelinated and unmyelinated afferents in the monkey but not in the cat. Nevertheless, no matter whether or not an anatomically distinct lateral division was present in the dorsal roots, bundles of fine afferent fibres from the dorsal roots eventually merged with Lissauer's tract (Snyder, 1977).

Lissauer (1886), for his part, considered that all the fibres in the tract were of dorsal root origin, an opinion that was soon challenged. Waldeyer (1888), Leszlenyi (1912) and particularly Nageotte (1903), stated that Lissauer's tract fibres were of endogenous origin, whereas Sottas (1893), Collier and Buzzard (1903) and Sibelius (1905) found limited degeneration in Lissauer's tract following lesions of the dorsal roots, thus implying a mixed nature of the tract (an excellent review of the earlier literature on Lissauer's tract can be found in Nathan and Smith (1959)). A problem linked to that of the origin of Lissauer's tract fibres was the recognition of their morphological characteristics. Although Ramón y Cajal (1899, 1909) mentions very fine fibres joining Lissauer's tract, the presence of many unmyelinated fibres in both the dorsal roots and the tract was brought to light by the extensive studies of Ranson (1913, 1914*a*, *b*). In these papers, Ranson described in detail the boundaries of the tract and its regional variations along the spinal cord, from a long and narrow bundle in cervical segments to a short and wide fascicle in the lumbosacral enlargement. Ranson confirmed the mixed derivation of Lissauer's tract fibres: most of those confined to the lateral part of the tract were of endogenous origin whereas those located in more medial areas were of dorsal root provenance. He also stated that most fibres of the tract were unmyelinated with some small myelinated fibres evenly distributed throughout the tract. Earle (1952) confirmed the division of Lissauer's tract into a mainly exogenous medial part and a lateral area formed by fibres of endogenous origin. He also added that the dorsal root fibre component was about 25 per cent of the total number of fibres which span not more than 1 or 2 segments in rostro-caudal direction. Szentágothai (1964) estimated a span of 1 to 3 segments for Lissauer's tract dorsal root afferents and of up to 5 to 6 segments for the endogenous fibres, which he definitely thought were axons of SG and marginal cells. Scheibel and Scheibel (1968) traced unmyelinated fibres from Lissauer's tract ending in the SG and suggested they were axons of other SG neurons. Réthelyi (1977) has produced similar and further evidence but attributed the SG endings to unmyelinated dorsal root afferents. La Motte (1977) also confirmed the presence of both endogenous and exogenous fibres in Lissauer's tract, spanning 1 to 3 segments in each direction. She distinguished two populations of afferent fibres in the tract: one ending primarily in laminæ II and III and another ending in lamina I and the outer regions of lamina II. She suggests that the former is made of unmyelinated dorsal root afferents and the other of small myelinated afferent fibres.

An independent opinion on the composition and fibre spectrum of Lissauer's tract was held by Wall (1962), and it was still maintained in recent publications of his research group (Merrill, Wall and Yaksh, 1978; Wall and Yaksh 1978; Wall *et al.*, 1979). Wall maintained that Lissauer's tract contained neither small myelinated fibres nor fibres of dorsal root origin. In more recent papers this opinion was modified by the inclusion of a few small myelinated dorsal root afferents. In any case the lateral part of Lissauer's tract was thought to contain only unmyelinated axons of SG neurons (Merrill *et al.*, 1978, Wall and Yaksh, 1978; Wall *et al.*, 1979).

A number of recent studies have greatly contributed to the resolution of these problems. Denny-Brown, Kirk and Yanagisawa (1973) reported changes in sensory dermatomal size after selective lesions of either the medial or the lateral divisions of Lissauer's tract in monkeys. This implies that axons of spinal cord neurons responsible for the integration of sensory inputs run in both areas of the tract and are not restricted to only one part. Moreover, Coggeshall's group (Chung, Langford, Applebaum and Coggeshall, 1979; Chung and Coggeshall 1979) have reported, in the first quantitative electron microscopical studies, the origin and calibre of Lissauer's tract fibres in the rat and the cat. From these studies it is now clear that the majority of the fibres in the tract are unmyelinated (80 per cent). About two-thirds of them are of dorsal root origin as are a similar proportion of the small myelinated fibres of Lissauer's tract. Thus, about one-third of the small myelinated and unmyelinated fibres in the tract are axons of superficial dorsal horn neurones (that is, 7 and 27 per cent of the tract, respectively).

An interesting outcome of the analysis by Coggeshall's group, confirmed in HRP studies of Lissauer's tract by Light and Perl (1979*a*, *b*), concerns the supposed segregation of endogenous axons in the lateral division of the tract. Both degeneration and HRP studies have shown that unmyelinated and small myelinated afferents are distributed throughout the tract, and although a higher concentration of primary afferent fibres seems to occur in medial parts of the tract this is by no means a consistent rule. Both afferents and endogenous axons, myelinated and unmyelinated, appear intermingled in all parts of Lissauer's tract in the cat and rat.

The present evidence concerning the anatomy of Lissauer's tract can be summarized as follows: (i) Lissauer's tract is principally composed of unmyelinated fibres (70 to 80 per cent), the remainder being thin myelinated fibres; (ii) both unmyelinated and small myelinated fibres are evenly distributed throughout the medial and lateral divisions of the tract in cat and rat; (iii) between one-third and a half of the fibres in the tract are dorsal root afferent fibres which run in the tract for 1 to 3 segments in both rostral and caudal directions; (iv) the remaining fibres are the axons of dorsal horn neurons, mainly marginal cells and SG neurons; (v) the total span of the endogenous fibres is still not clear but estimates range between a few millimetres and 5 to 6 segments; (vi) although there is a preferential location of endogenous axons in the more lateral areas of the tract, endogenous and exogenous fibres are intermingled throughout its whole extent.

V. *Peripheral Inputs to Marginal and Substantia Gelatinosa Neurons*

Morphological studies on the afferent inputs to SG neurons have mainly been concentrated on analysis of the dorsal root projection to the area. Even before the first structural details of the SG were described, the proximity of the SG to the dorsal root entry led to the proposal that dorsal root fibres relay in the SG (van Deen, 1841). A plexus of horizontal fibres in the superficial SG together with numerous nerve fibres of dorso-ventral orientation was clearly illustrated by Clarke (1859) and Stilling (1859*a*). The dorsal root origin of these fibres was suggested by Kölliker (1860) and doubted by Lenhossék (1895). Ramón y Cajal (1899, 1909) produced a comprehensive picture of the dorsal root input to the SG which is still generally valid. According to Cajal, the SG received two kinds of afferent input: a projection of thick fibres coming from the ventral side of the SG and a dorsal projection of thin fibres. The thick fibres enter the dorsal horn from the adjacent dorsal columns, take an initial ventral direction and curve suddenly to reach the SG from below. These fibres, which Cajal clearly thought were of dorsal root origin, end in a characteristic profuse arborization which the Scheibels (1968) very aptly named 'flame-shaped arbors'. The second fibre projection was formed by numerous fine fibres entering from the dorsal aspect of the SG from Lissauer's tract and other propriospinal tracts. Since many of these fibres came from Lissauer's tract, Cajal was not as certain of their dorsal root origin as he was about the thick fibres. The fine fibres in entering the dorsal aspect of the SG branched in a complex plexus of intermingled terminal arborizations. Cajal also described a plexus of fine fibres in the marginal zone (the marginal plexus) making contacts with the large marginal cells. Most of these fibres were traced back to Lissauer's tract. Their dorsal root origin was suggested although the possibility that some fibres were of propriospinal origin was left open. Cajal's scheme was implemented by Ranson (1913, 1914*a*, *b*) who studied in particular the projection of small myelinated and unmyelinated fibres from the dorsal roots, through Lissauer's tract to the SG. Ranson concluded that the marginal plexus contained both small myelinated (i.e. Aδ) and unmyelinated (i.e. C) afferent fibres, whereas the SG received an exclusively unmyelinated dorsal root projection. Szentágothai (1964) confirmed the classical views of Cajal on the organization of the afferent input to the SG, although he held the opinion that many of the fine fibres ending in the SG were in fact axonal arborizations of SG neurones.

Szentágothai's implementation of Cajal's observations and the didactic blueprints of the SG that he produced (Szentágothai, 1964) were firmly established in the literature as references to the morphological organization of the superficial dorsal horn. In the fifteen years since their publication, a number of issues have been brought to discussion resulting in important re-examinations of the distribution of dorsal root fibres to the SG and marginal zone. Three questions are particularly relevant: (i) the origin of the fine fibres of the SG; (ii) the existence of endings of thick dorsal root afferents within the boundaries of the SG and (iii), the detailed organization of the synaptic glomeruli which are a prominent feature of the neuropil of the SG.

Projection of dorsal root fibres to the SG was denied by Ralston (1965, 1968*b*) and Sterling and Kuypers (1967). Ralston traced numerous bundles of small unmyelinated axons ($< 1\ \mu m$) in the SG, with many endings or 'en passant' boutons. Following section of the dorsal roots he could not find degeneration of these terminals in lamina II (the SG) although degenerated axons were plentiful in lamina III. Ralston (1965, 1968*b*) concluded that the rich network of unmyelinated axons in the SG was produced by the branching of the axons of SG neurons; an opinion also held by the Scheibels (1968). In contrast with this, Heimer and Wall (1968) found massive degeneration in laminæ I to III following dorsal root section and stressed the point that the time course of the degeneration in lamina II differed from that in lamina III. A recent re-examination of the problem by Ralston and Ralston (1979) has confirmed Heimer and Wall's observations.

Following dorsal rhizotomy, degeneration first occurs in the largest myelinated afferents present in the inner portion of the SG, although mainly distributed in lamina III. Next follows degeneration of small myelinated afferents in lamina I and the outer portion of lamina II and finally there is degeneration of the unmyelinated afferent fibres present exclusively in both portions of lamina II (Ralston and Ralston, 1979). This study offers a clear explanation of the conflicting evidence from earlier degeneration studies and also presents a more complete picture of the distribution of dorsal root afferents of different kinds to the SG and adjacent areas. It is clear then, that some of the fine collaterals entering the SG from its dorsal side are of dorsal root origin (Réthelyi and Szentágothai, 1973), but it is also firmly established that other neuronal elements, particularly axons of SG neurons, contribute to this projection. Beal and Fox (1976), in an extensive study of the fibres of the SG, concluded that the fine fibre component could be divided on morphological grounds into two groups, the fibres giving either fine terminal branches or large and irregular endings. The former were suggested to be axons of

SG neurons, and the latter to be endings of fine dorsal root afferents. Both sets of fine fibres were confined to the boundaries of lamina II (Beal and Fox, 1976). Narotzky and Kerr (1978) analysed the neuropil of the marginal cells and concluded that the superficial plexus of fibres (the marginal plexus) contains fine dorsal root afferents ending on the distal dendrites of marginal cells and axons of SG neurons with terminal boutons over the somata and proximal dendrites of the flat marginal neurons. On the other hand, Réthelyi (1977) has analysed the geometry of the non-myelinated fibre input to the SG and examines arborizations that he believes are from dorsal root C-fibres. This particular kind of ending offers a peculiar geometry, with terminal boutons distributed along the whole dorso-ventral extent of lamina II (150 μm) in a very narrow medio-lateral (16 to 26 μm) and extremely long rostro-caudal (up to 1000 μm) orientation. These endings form a nearly two-dimensional longitudinal arrangement which matches closely the extent of the dendritic arborizations of 'central type' SG neurons. The origin of these structures from unmyelinated fibres has been questioned by Gobel and Falls (1979), who found that many of the fine arborizations in lamina II are in fact connected to parent dorsal root axons having diameters of 1 to 1.5 μm, that is, of small Aδ fibres. On the basis of present knowledge we can conclude that the marginal zone (lamina I) contains mainly Aδ dorsal root fibres and axons of SG neurons ending on marginal cells, whereas the SG (lamina II) is the main nucleus of reception for peripheral C-fibres. Axons of SG neurons and Aδ dorsal root fibres are also present in the SG (lamina II). The latter are particularly distributed over the inner portions of the SG.

A second question currently under discussion is whether or not endings from large dorsal root fibres penetrate the SG (lamina II). The Scheibels (1968) confidently claimed that these endings (flame-shaped arbors) penetrated the whole lamina III, most of lamina II and that some even reached lamina I. The radial orientation of these endings was held responsible for the lobular appearance of the SG (Szentágothai, 1964). In recent years these observations have been called to question. La Motte (1977) found that large afferents from the dorsal roots end only in laminæ IV to VI, an observation substantiated by Hamano, Mannen and Ishizuka (1978) who stated that dorsal root afferents with diameters greater than 1 μm rarely penetrate lamina II.

Similar observations were reported by Ralston and Ralston (1979) but Proshansky and Egger (1977*b*), using aterograde transport of HRP from cut dorsal rootlets, could see endings of 'flame-shaped arbors' reaching the ventral side of lamina II. Beal (1979), in a Golgi study, is also of the opinion that the terminals of some deep fibres reach the inner SG, although, in a previous publication (Beal and Fox, 1976) it was stated that the endings of large dorsal root fibres (named 'confined ansiform axonal complexes') were mainly found in lamina III, and that their present in lamina II was much less frequent.

The technique of intracellular staining of physiologically identified dorsal root fibres with HRP has added new perspectives to the question. Brown *et al.* (1977*b*, 1978) reported that the 'flame-shaped arbors' are the terminals of hair follicle afferent units, and that they are distributed mainly over laminæ III and IV with rare incursions to the ventral region of lamina II. Similarly, terminals of slowly-adapting type I cutaneous receptors (Iggo and Muir, 1969) end below the SG, and are confined to laminæ III, IV and V (Brown *et al.*, 1978). Light and Perl (1979*a*) re-examined the projection of dorsal root fibres to the superficial dorsal horn, using anterograde transport of HRP applied to the roots. They concluded that Aδ fibres end in laminæ I and III, with some projecting to the inner lamina II, that C-fibres terminate exclusively in the SG proper (lamina II) and that endings from large myelinated fibres do not ascend beyond the dorsal border of lamina III. Intracellular staining of individual Aδ dorsal root fibres shows further segregation (Light and Perl, 1979*b*). Fibres taking origin from mechanical nociceptors end in laminæ I and V, whereas those coming from 'D' hair follicle receptors and connected to Aδ afferent fibres distribute along lamina III and the ventral side of lamina II, either as 'flame-shaped arbors' or by giving off collaterals directly to those areas. (fig. 1).

It seems, then, that the whole argument on the organization of the dorsal root projection to the SG and other superficial layers of the dorsal horn lies in the lack of agreement on the 'permeability' of the borders between different laminæ. If one takes the view that the SG and other layers are areas or zones of projection with transitional borders between them, the whole issue becomes much less tangled and perhaps less emotive and can be summarized as follows (*see* fig. 1 for anatomical details): (a) the marginal zone receives extensive projection of dorsal root Aδ fibres, but arborizations of SG axons and dorsal root C-fibres can reach neurons in this area; (b) the SG is the main, if not the only, nucleus of reception for dorsal root unmyelinated fibres, but terminal arborizations of Aδ and Aβ dorsal root fibres can reach its ventral aspect in small numbers and (c), the bulk of the projection of large myelinated dorsal root afferents seems to be confined to laminæ III, IV and V.

A third question which has been discussed in recent years relates to the organization of the SG neuropil, and in particular, the synaptic arrangement of the 'glomeruli'. One important element in Cajal's schemes of the SG was the presence in the SG of numerous dendrites from deeper dorsal horn neurons that intermingled there with SG neurons and dorsal root fibre terminals. This feature was implemented by Szentágothai (1964) and the Scheibels (1968) in their schema. It has remained a constant feature of all descriptions of the relationship between SG neurons and larger and deeper cells, particularly those in lamina IV (Réthelyi and Szentágothai, 1973). Proshansky and Egger (1977*a*) studied the dendritic spread of neurons in laminæ IV, V and VI and reinforced the view that lamina IV neurons project dorsal dendrites to lamina III and the SG. Now that individual neurons are being stained intracellularly, and their dendritic organization analysed in detail, the picture is beginning to change. Brown *et al.* (1976, 1977*b*) stained spino-cervical tract neurons with procion yellow and with HRP. These neurons have somata located mainly in lamina IV with fewer in laminæ III or V. Brown's group have reported that dorsal dendrites of spino-cervical tract neurons rarely penetrate the SG (lamina II), and very often, on reaching the ventral border of the SG, turn and run along the longitudinal axis of the cord. In a sample of two SCT neurons, Rastad, Jankowska and Westman (1977) reported one cell with dendrites confined to laminæ III and IV and another with the soma in lamina III and a few dorsal dendrites penetrating the ventral SG. It seems, therefore, that the classical concept of dendrites of deeper dorsal horn neurons (particularly those in lamina IV) penetrating the whole extent of the SG and being a conspicuous feature of its neuropil is invalid. Nevertheless, there are neurons other than spino-cervical tract cells in lamina IV (such as dorsal column postsynaptic units) whose dendritic arborizations, as revealed by HRP injections, may penetrate both the SG and the marginal layer (Brown and Fyffe, 1980). At this point it is worthwhile to go back to the initial description of the SG and remind ourselves that the border between the SG and the rest of the dorsal horn was clearly depicted, in the splendid figures of Clarke (1859) and Stilling (1859*b*), as a band with many bundles of fibres that stopped suddenly at the ventral edge of the SG. This band is today's lamina III, a region that contains the endings of large cutaneous afferents and the dendritic trees of those neurons in lamina IV that do not cross the ventral border of the SG.

A typical feature in the neuropil of the superficial dorsal horn is the presence of synaptic arrangements called 'complex synaptic arrays' by Ralston (1965), 'large synaptic complexes' by Réthelyi and Szentágothai (1969) and 'glomeruli' by Kerr (1966, 1975). The term 'glomerulus' seems to be simple and descriptive enough to be widely used and will be adopted here. The glomerulus consists of a central and enlarged synaptic bouton covered by numerous smaller processes which establish various synaptic contacts between themselves and the central bouton. The central bouton was regarded as an axonal ending from a special kind of neuron whose soma was in lamina III (Réthelyi and Szentágothai, 1969), but this view has been abandoned because the central boutons degenerate following dorsal rhizotomy (Coimbra *et al.*, 1974). The interest in the synaptic glomeruli can be traced to the proposal that SG neurons mediate dorsal root potentials by acting presynaptically on endings of dorsal root afferents (Wall, 1962). Glomeruli could offer the ultrastructural basis for such axo-axonal contacts between the endings of SG axons (peripheral processes) and the dorsal root afferents (central boutons). The number of arrangements proposed for the synaptic circuitry of the glomeruli is not small (*see* Willis and Coggeshall (1978) for an excellent review). Once again the lack of a common nomenclature has made a contribution to the conflicting evidence. Synaptic glomeruli are present in lamina III (included by some authors in the SG), where they probably represent the synaptic contacts between dorsal root afferent terminals and dendrites of laminæ III and IV neurons. In lamina II (that is, in our view, the SG) the glomeruli become less frequent and their central boutons are almost certainly endings of dorsal root C-fibres (*see* Csillik and Knyihar, 1978). Beal and Fox (1976) were of the opinion that the glomeruli of lamina II (the SG) were formed by the large irregular endings of fine dorsal root fibres, whereas those in lamina III resulted from the terminal endings of the 'confined ansiform axonal complexes' generated by thick myelinated dorsal root afferents. Because of their

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peculiar morphology, glomeruli have probably been over-estimated as representatives of the synaptic arrangement in the SG. Counts of synaptic profiles show that glomeruli make up only 5 per cent of the synapses in the SG. Moreover, Duncan and Morales (1978) reported that 97 per cent of the synapses on the SG, 'glomerular' or 'extraglomerular', were axo-dendritic, an observation recently substantiated by Ralston (1979). If this is so, glomeruli are simply a morphological variant of traditional synaptic contacts between dorsal root fibres and dendrites of neurons in the SG, lamina III and lamina IV. The large numbers of extraglomerular contacts suggest a good deal of intra-SG connectivity, but the issues of axo-axonic synapses and the ultrastructural basis of presynaptic inhibition seem to have lost interest, at present.

VI. *Intraspinal and Supraspinal Inputs to Marginal and Substantia Gelatinosa Neurons*

The presence of extensive intraspinal projections to marginal and SG neurons has already been indicated in previous paragraphs. As far as the large marginal cells are concerned it seems that their only intraspinal input comes from axonal projections of SG neurons. These axons contribute to the dense marginal plexus and eventually end on the somata and proximal dendrites of marginal cells (Narotzky and Kerr, 1978).

The SG, for its part, receives a considerable projection of fine fibres of intraspinal origin. Most of them are axonal terminal arborizations from other SG neurons establishing short (2 to 3 mm) or long (up to 5 to 6 segments) intra-SG connections. Axonal projections of SG neurons have been traced to the marginal zone, to the SG itself (lamina II) and to lamina III (Ramón y Cajal, 1899, 1909; Szentágothai, 1964; the Scheibels, 1968; Matsushita, 1969). According to Beal and Fox (1976) terminals of SG axons have a distinct morphology which differs from that of the endings of dorsal root afferent fibres. The regional distribution of these intraspinal projections and their suggested origin indicates that SG neurons may establish connections with marginal and other cells in the marginal zone, with other SG neurons in lamina II and, because of their projection to lamina III, with neurons in this lamina and with dorsal dendrites of lamina IV neurons. Other sources of intraspinal inputs to the SG are the marginal cells. It has been indicated already that the axons of marginal and other neurons in the marginal zone give off a few collaterals which arborize within the limits of the SG, although evidence is lacking for direct connections between axon collaterals of marginal cells and SG neurons. The relative importance of such a projection is also unknown, but the anatomical evidence suggests the existence of feedback and integrative neuronal circuits between marginal and SG neurons.

Peripheral and intraspinal inputs to the SG constitute a substantial proportion of the total inflow to its neuronal elements. In recent years the attention of morphologists and physiologists has turned to the study of possible inputs to the superficial dorsal horn from supraspinal structures. Traditionally, descending control was thought to be exerted chiefly on spinal reflexes through actions on the motoneuronal pools. It is now established that sensory pathways are also under strong control from supraspinal structures. There is a good deal of functional study on descending influences on dorsal horn neurons, including marginal and SG neurons, but less attention has been paid to their morphological aspects. Current anatomical evidence on such projections comes almost exclusively from studies using histochemical techniques or modern methods of tracking nervous pathways, such as HRP or autoradiographic studies.

A major source of descending control on sensory pathways is the pyramidal tract. Detailed HRP studies have, however, shown that in the monkey direct corticospinal projections are restricted to laminæ IV, V and VI, with a few endings reaching the ventral side of lamina III (Coulter and Jones, 1977). Most, if not all, descending pathways ending in the SG and marginal zone take origin in the brain-stem, particularly in or around the raphé nuclei (Bobillier, Seguin, Petitjean, Salvert, Touret and Jouvet, 1976; Basbaum, Clanton and Fields, 1976, 1978; Martin, Jordan and Willis, 1978; Fields and Basbaum, 1978).

Dahlström and Fuxe (1964) and Crutcher and Bingham (1978), using histochemical methods for the detection of catecholamine-containing terminals, found numerous monoaminergic endings in both the marginal zone and the SG and a less extensive projection to other areas of the dorsal horn. Most monoaminergic terminals disappear after lesions of the locus coeruleus, but not those found in the marginal zone and the SG (Nygren and Olson, 1977).

Recent autoradiographic studies offer a comprehensive view of the brain-stem projection to the dorsal horn. Basbaum *et al.* (1978) studied three bulbo-spinal pathways from the rostral medulla and originating in the nucleus reticularis gigantocellularis (NRGc), the nucleus raphé magnus (NRM) and the nucleus reticularis magnocellularis (NRMc). Pathways originating in NRGc course in the ventral funiculi of the cord and end in the ipsilateral and contralateral ventral horns, particularly in laminæ VII and VIII. In contrast, the spinal projection from NRM and NRMc affects more superficial areas of the cord, *via* pathways coursing in the dorso-lateral funiculus that end in laminæ I, II, V, VI and VII. Projections from NRM are bilateral, whereas that from NRMc is exclusively ipsilateral.

There is therefore evidence, albeit incomplete, of the existence of brain-stem projections to the SG and marginal zone. This projection is by no means exclusive. Other areas of the dorsal and ventral horn containing the cells of origin of ascending pathways also receive extensive projections from similar areas of the brain-stem as well as selective descending projections from other brain-stem and cortical regions.

VII. *Comparative Studies on the Substantia Gelatinosa*

Most morphological observations reported in the preceding pages come from studies of the cervical and lumbar enlargements of cat, monkey, rat and, more rarely, human spinal cords. Mention of the few systematic regional and phylogenetic studies on the SG may serve to arouse interest in this relatively neglected aspect of the anatomy of the nervous system.

Descriptions of regional variations in the size and shape of the SG along the spinal cord are common in early reports. Clarke (1859) studied the cord of several species of reptiles, birds and mammals; Waldeyer (1888) described one specimen of gorilla's spinal cord from cervical to caudal segments and compared it with a child's cord; human spinal cords were studied from end to end by Bruce (1901), Jacobsohn (1908) and Massazza (1922–1924), whereas Rexed (1954) analysed the regional variations of the spinal cord of the cat. Most of these studies are protracted narratives of external or internal features of the specimens in question. As far as the SG is concerned there is consensus on its continuous extension along the whole length of the cord and the close relation between the total grey matter and the extent of the SG in a given segment. A numerical study on the regional variations of the SG along the cords of 25 species of mammals (Sano, 1909) showed that the SG is largest in sacral segments, and next largest in the cervical and lumbar enlargements. At thoracic levels the SG is much less extensive, but since the total grey matter in these segments is also small, the relation between grey matter and SG is kept constant (Sano, 1909). The dorsal horns of both sides are fused at thoracic and caudal segments. In these two regions the SG is continuous from side to side in contrast to its well-defined and independent disposition in cervical, lumbar and sacral segments (Clarke, 1859; Bruce, 1901; Jacobsohn, 1908; Rexed, 1954).

An interesting detail in the regional variations of the SG concerns its organization in sacral and sacro-caudal segments. These regions of the cord have been extensively used by E. R. Perl's group in their physiological studies of the marginal zone and the SG. Most authors noted that at sacro-caudal levels the marginal zone is larger than elsewhere in the cord and contains numerous marginal cells. This thick marginal zone curves around the dorsal horn and encircles completely the sacro-caudal SG (Waldeyer, 1888; Massazza, 1922–1924; Rexed, 1954). Many marginal and limiting cells are present at these levels and some intermingle with the small neurons of the enclosed SG (Massazza, 1922–1924). The number of marginal cells decreases in lumbar segments as the thick marginal zone becomes the thin veil of grey matter typical of the lower lumbar cord. The SG also changes in the most caudal areas of the cord from a cylindrical structure in caudal segments to a kidney-shaped band in sacral segments and finally to the characteristic curved band of lumbar regions (*viz.* Rexed, 1954).

A different kind of comparative study is that of phylogenetic variations. The SG has been studied in many animal species from sharks to elephants, but the only phylogenetic study known to us is that of Keenan (1928, 1929*a*, *b*). Keenan studied 53 species of fish, 10 of amphibians, 9 of reptiles, 18 of birds and an unspecified number of mammals. He concluded that the SG is present throughout the whole vertebrate phylum, but this statement must be taken with caution. True SG can only be defined on the basis of its characteristic microscopic appearance, cell population and afferent input. On these bases SG or SG-like formations exist in mammals, birds (Brinkman and Martin, 1973; Leonard and Cohen, 1975) and amphibia (Szekely, 1976; Sasaki, 1977). Because of the peculiar organization of the spinal cord of fishes (Nieuwenhuys, 1964) it is almost certain that these animals do not have a true SG, although electron microscopy studies show that an SG of a more reticular distribution is present in some species of fish (K. H. Andres, personal communication).

The SG seems to be present in all mammals, with the apparent exception of Cetacea (Kappers *et al.*, 1936). An extensive comparative study of the SG by Sano (1909) of 25 mammalian species from koala to orang-utang found no well-defined lines of development which might give a clue to a specific function of the SG. The often quoted statement that the SG is developed most highly in ungulates seems to be unwarranted by solid anatomical evidence.

Regional and phylogenetic studies of the SG were once fashionable and seem now to be nearly forgotten. Yet the available information from old reports is highly inconclusive and much useful knowledge could be gathered from proper comparative re-investigation. Here is, perhaps, a line for a future approach to the SG.

PHYSIOLOGY OF THE SUBSTANTIA GELATINOSA

I. *The Substantia Gelatinosa as a Sensory Nucleus*

Present ideas on the functional organization of the spinal cord originate from the discovery of the function of the spinal roots. The first half of the 19th century was dominated by the discovery of the anatomical dissociation of sensory and motor functions at the spinal cord entry and the emotions resulting from the dispute between Bell and Magendie. The success of the Bell-Magendie proposal is easily judged by the extension of the dorso-ventral functional dissociation to many other structures of the nervous system. Being the first nucleus reached by the dorsal roots, the SG was soon implicated in sensory mechanisms.

A comprehensive treatise on the physiology of the spinal cord, published by van Deen in 1841 presented for the first time a functional interpretation of the SG. He proposed that the SG acts as a junctional point in the pathways for sensory transmission and reflex action. Sensory impulses reach the SG *via* the dorsal roots and can then take two routes: to the sensorium *via* the dorsal columns or to the muscles *via* the ventral horn and roots. In spite of their simplicity, van Deen's ideas still form a basic framework of current thought on spinal cord functions.

Van Deen's proposals were general and non-specific and subsequently more attention was paid to the detailed study of the SG cells themselves than to their place in general functional design of the nervous system. Because of their small size and great numbers, SG cells were thought to be part of the 'connective tissue of the spinal cord' (Clarke, 1859), neuroglial elements (Owsjannikow, 1854; Stilling, 1859*a*) or neurons in embryonic state (Lenhossék, 1889). Golgi (1890) and Ramón y Cajal, (1890, 1891) advocated their neuronal nature, based on the morphological features of SG cells and their similarities to those of other neuronal elements.

In consequence, by the beginning of the 20th century, SG cells were considered local interneurons in the sensory systems of the spinal cord (Rosenzweig, 1905; Jacobsohn, 1908; Ramón y Cajal, 1909). The only contrary opinion was expressed by Sano (1909) who, on the basis of extensive comparative studies, proposed that the SG was linked to the autonomic nervous system and that its cells had a vasomoter function.

The substantia gelatinosa and pain. The detailed morphological and functional studies of the dorsal roots and SG by Ranson and his associates (Ranson, 1913, 1914*a*, *b*; Ranson and von Hess, 1915; Ranson and Billingsley, 1916) led to the direct implication of the SG in the mechanisms of pain transmission through the spinal cord. There were two main observations: (i) the SG receives most, if not all, of the small myelinated and unmyelinated afferent fibres from the dorsal roots *via* the lateral division of the roots and Lissauer's tract. This observation came at a time when von Frey's ideas on the specificity of cutaneous receptors were influential (von Frey, 1895) and when unmyelinated fibres with bare nerve endings were generally thought to be the 'pain fibres'; (ii) section of the lateral division of the dorsal roots, carrying fine afferents to the SG, resulted in the abolition of vasomotor and respiratory reactions typical of reactions of painful stimuli (pseudo-affective reflexes of Sherrington (1906)).

The picture that emerged from Ranson's observation is very well depicted in the paper of Earle (1952) and Pearson (1952): 'pain fibres' relay in the SG on to neurons that converge on spino-thalamic tract neurons which carry the 'pain impulses' to the higher centres of the nervous system. It is not unusual to find this kind of statement in current textbooks.

A further elaboration on the role of the SG in pain mechanisms was proposed in the 'gate control theory of pain' by Melzack and Wall (1965). The reader is referred to an excellent critical review in *Brain* by Nathan (1976), for a general consideration of the place of this theory in the development of ideas on the mechanisms of pain. The 'gate theory' is relevant to the present article in so far as it proposed a particular function, albeit hypothetical, for the SG neurons and a more general conceptual role for the SG as a nucleus with modulatory actions on sensory transmission. The SG, coming between the sensory input to the spinal cord and the ascending sensory pathways was postulated to function as 'a gate control system'. Experimental evidence implicating the SG in modulatory spinal action, at the time of the publication of the 'gate theory', came from a study of Wall (1962), who reported that the dorsal root potential was dependent on the integrity of Lissauer's tract and thus was generated by activity in the SG neurons. The dorsal root potential had been described by Barron and Matthews in 1938 and was later thought to be an indication of presynaptic inhibition (Eccles, Schmidt and Willis, 1963). The 'gate theory' model proposed a presynaptic inhibitory control by the small SG neurons of transmission through the first spinal synapse. Melzack and Wall (1965) also suggested that other mechanisms might be implicated, but since the only experimental evidence at the time was of presynaptic inhibition this particular system was the one depicted in the diagram of the 'gate control' model.

The role of the SG neurons in the generation of dorsal root potentials and the 'gate theory' itself, have met a good deal of adverse criticism (*see* Schmidt, 1971, and Nathan, 1976). Nevertheless the model focused the attention of many research workers on the SG and the mechanisms of sensory modulation in the dorsal horn. Thus the SG regained its putative 19th century role (*see* von Deen, 1841) in controlling or modulating all sensory information passing through the dorsal horn, and not only those inputs related to nociception and pain.

The work of Denny-Brown *et al.* (1973) predicated a general modulatory function for SG neurons with both excitatory and inhibitory effects on dorsal horn transmission neurons. This conclusion was reached by observing changes in sensory dermatomal size on monkeys following localized lesions in Lissauer's tract. Their study signalled the end of indirect analysis of the function of SG neurons and provided a new and firm conceptual base for more direct attempts to record single unit activity from the small SG neurons. This latter aspect will be dealt with in detail in the following sections.

Afferent input to the spinal cord. The conceptual framework for the experimental analysis of the spinal cord sensory mechanisms is determined by the theoretical concepts of the nature of the sensory inflow. Sensory hypotheses based on a temporo-spatial coding of receptor activation (Weddell and Miller, 1962) led to a search for de-coding mechanisms that read the code in terms of the order, frequency and duration of impulse patterns across the population of afferent fibres. The 'gate theory of pain' is an example of this approach. Hypotheses based on a specialization of receptors, so that there is a greater or lesser degree of specificity in the afferent units (the so-called classical specificity theory), going back even to Müller's doctrine of specific nerve energies (Müller, 1840) seek instead for dorsal horn neurons responding to an afferent input in specified afferent units. This approach requires quantitative control of natural stimuli delivered to the receptors (as by movement of hairs, indentation of the skin, temperature changes) arranged as far as possible to minimize the use of confusing input signals. For example, radiant heat can be used to excite nociceptors with minimal simultaneous excitation of sensitive mechanoreceptors, although not without altering the afferent input from sensitive thermoreceptors. A second requirement of this analytical approach is that the investigator has adequate knowledge of the characteristics of the peripheral sensory receptors. Brown's (1971) analysis of the spino-cervical tract neurons is an excellent example of this approach.

The weight of evidence is now overwhelmingly in favour of the specificity hypothesis (*see* Burgess and Perl, 1973; Iggo, 1974). Firm morpho-functional correlations are now established for the cutaneous mechanoreceptors (Iggo, 1974), and for some cold receptors (Hensel, Andres and von Düring, 1974). Of particular interest for the present review is the position of the small myelinated and the non-myelinated afferent fibres that run into the superficial dorsal horn. Single unit afferent fibre studies have now established that the small myelinated (that is, Group III or Aδ) cutaneous afferents include sensitive mechanoreceptors (type D hair receptors (Brown and Iggo, 1967) and mechanical nociceptors (Burgess, Petit and Warren, 1968) in the cat, and these kinds plus sensitive cold receptors in primates (Iggo, 1963, 1969; Perl, 1968). The non-myelinated cutaneous afferent units also comprise a diversity including sensitive C-mechano-receptors (Iggo, 1960; Iggo and Kornhuber, 1977), cold and warm receptors (Hensel, Iggo and Witt, 1960; Iggo, 1969) and several kinds of nociceptor (Iggo, 1959; Bessou and Perl, 1969; Beck, Handwerker and Zimmermann, 1974). These conclusions based on detailed quantitative studies in laboratory animals are now being confirmed in man by the techniques of percutaneous microelectrode recording from peripheral nerves in conscious subjects (*see* Zotterman, 1976 for a recent symposium). These cutaneous afferent fibres are joined by muscles, joint and visceral afferents (Iggo, 1966; Leek, 1977; Mense, 1977) so that the superficial dorsal horn (laminæ I–III) receives a remarkably rich and functionally diverse afferent input.

II. *Physiology of the Marginal Zone*

The first report of electrophysiological studies in the marginal zone was made by Wall (1968). In a review article he concluded that he had made extracellular recordings of electrical activity from the Waldeyer cells of the marginal zone. Quoting results from spinal animals, Wall reported that these neurons were spontaneously active, monosynaptically connected to large cutaneous receptive fields and extremely non-specific in their functions, since they responded to many types of cutaneous, muscle and joint afferents. In view of this he took 'the risk of neglecting the rôle of these cells in the functioning of the deeper layers' (Wall, 1968).

Two years later an entirely different picture of the functional responses recorded in the marginal zone emerged from the publication of Christensen and Perl (1970). In spinal cats they explored the superficial dorsal horns of sacral and coccygeal segments and found a heavy excitatory projection to these regions by small Aδ and C afferent fibres. They reported extracellular unit recordings in the marginal zone and attributed them to activity of the somadendritic portions of neurons. Three groups of units were described: (i) units responding only to nocuous mechanical stimulation of the skin; (ii) units responding to nocuous mechanical and thermal stimulation of the skin and (iii) units responding to intense mechanical and nocuous heat stimuli, and, in addition, to innocuous temperature changes of the skin. On the basis of extracellular dye marking they concluded that unitary responses were recorded from the large marginal cells (Waldeyer cells), and, on the basis of the physiological results, that these neurons were relevant to the mechanisms of nociception and temperature detection.

This initial report of Christensen and Perl was later substantiated and extended by studies from many laboratories. Cervero, Iggo and Ogawa, (1976) reported extracellular recordings in the marginal zone of anæsthetized cats from specific nociceptor-driven neurons (Class 3 dorsal horn neurons in their nomenclature). They divided the population of Class 3 cells into two groups: (i) 3a, responding only to nocuous mechanical stimuli of the skin and (ii) 3b, responding to both mechanical and thermal nocuous stimuli of the peripheral receptive fields. The class 3b neurons were also activated by electrical stimulation of Group III and IV muscle afferent fibres.

Confirmatory reports regarding the existence of a population of specific nociceptor-driven neurons in the marginal zone have been published. These come from experiments on cats, monkeys and rats using a variety of preparations (Willis, Trevino, Coulter and Maunz, 1974; Handwerker, Iggo, Ogawa and Ramsey, 1975; Kumazawa, Perl, Burgess and Whitehorn, 1975; Kumazawa and Perl, 1976; Menetrey, Giesler and Besson, 1977; Mitchell and Hellon, 1977; Kumazawa and Perl, 1978; Necker and Hellon, 1978; Applebaum, Leonard, Kenshalo, Martin and Willis, 1979). A picture emerges of a homogeneous population of marginal zone neurons, that have little background activity, relatively small receptive fields, an excitatory drive from skin and muscle nociceptors and segmental inhibition from fast conducting low threshold cutaneous afferents. Two major issues which need further clarification are: (i) the existence in the marginal zone of neurons other than the specific nociceptor-driven cells (Class 3) and (ii), the morphological substrate of the Class 3 neurons, namely, whether or not all Class 3 neurons are the Waldeyer cells of the marginal zone.

Non-specific neurons in the marginal zone. As regards the first issue it has already been mentioned that Christensen and Perl (1970) described neurons excited by innocuous thermal stimuli as well as by severe or nocuous stimuli. Similar, but more selective, neurons have also been found in rats and monkeys (Hellon and Misra, 1973; Iggo and Ramsey, 1976) but very seldom in cats. On the other hand Handwerker, Iggo, Ogawa and Ramsey (1975) in the monkey, Cervero *et al.* (1976) in the cat and Menetry *et al.* (1977) in the rat, have described recordings in the marginal zone from neurons excited by nocuous and innocuous stimulation of the skin (Class 2 cells). Since these are extracellular recordings it is not possible to decide whether the activity came from cell bodies or from axons of Class 2 neurons located deeper in the dorsal horn and traversing the superficial dorsal horn on their way to join ascending pathways in the dorso-lateral funiculus or the dorsal columns (Brown *et al.* 1976). In recent studies of SG neurons, also using extracellular recording, responses typical of Class 2 neurons have been reported not only in the SG proper (lamina II) but also in the more superficial marginal zone (lamina I) (Price, Hayashi, Dubner and Ruda, 1979). One corollary of the existence of Class 2 neurons in the marginal zone is that the low threshold cutaneous input must necessarily be polysynaptic, since it seems well established that the marginal zone is free from endings of large myelinated afferent fibres. In any case, the possible existence of Class 2 neurons in lamina I does not diminish the importance of the well documented existence of the population of specific nociceptor-driven cells in the marginal zone. Indeed, it reinforces the idea that the dorsal horn is a concatenation of different neurons.

Morphology of neurons. The presence of different functional types of neurons (Class 2 and 3) in the marginal zone brings up the second major issue regarding the physiology of this area: the morphological identification of the type of cell from which electrophysiological responses were recorded.

Christensen and Perl (1970) reached the conclusion that their recordings were from Waldeyer cells because of the relatively larger size of these neurons, and thus the greater chance of recording from them with conventional microelectrodes, and on the presence of Waldeyer cells in the near vicinity of their extracellular dye marks. On this evidence it has been generally assumed that Class 3 cells in lamina I are Waldeyer cells. Yet, electrophysiological studies of the marginal zone have shown that there is a lack of uniformity in the population of Class 3 cells in lamina I in so far as the destinations of their axons are concerned. Kumazawa *et al.* (1975) in cats and monkeys, Handwerker, Iggo, Ogawa and Ramsey, (1975) in monkeys, and more recently Cervero, Molony and Iggo (1979*a*) in cats, reported that only one-third to one-half of the nociceptor-driven cells in lamina I could be antidromically activated from more rostral segments of the cord. Therefore, as many as 60 per cent of Class 3 cells in lamina I are segmental or local interneurons.

These results, furthermore, are inconsistent with classical concepts about Waldeyer cells. They are defined by Ramón y Cajal (1909) as projecting neurons. Kuru (1949) found retrograde chromatolytic reactions in marginal cells in patients after antero-lateral cordotomies and studies using retrograde transport of HRP show that Waldeyer cells project to the thalamus in the cat (Trevino and Carstens, 1975; Carstens and Trevino, 1978), rat (Giesler *et al.*, 1979) and monkey (Trevino, Couller and Willis, 1973; Willis *et al.*, 1979). Additional types of neuron in the marginal zone are also filled with HRP following injections in the thalamus (Willis *et al.*, 1979). However, the 'pyriform', 'triangular' or 'fusiform' marginal cells they describe are possibly only varieties of the better known classical type of Waldeyer cell. Very similar cells were actually described as Waldeyer cells by Lenhossék in 1895.

The body of morphological evidence thus points to the marginal or Waldeyer cell as a neuron with a long axon projecting rostrally. In view of this we make the following proposal: (i) all Waldeyer cells (also called marginal cells) are neurons projecting through one (or more) or several sensory ascending pathways, namely, the spinothalamic tract, spinoreticular tract, spinocervical tract and the dorsal column postsynaptic pathway. The pathway of projection varies according to species; (ii) Waldeyer cells are either specific nociceptor-driven neurons (Class 3) or specific thermoreceptor-driven neurons (in some species and locations); (iii) many of the Class 3 cells in lamina I as well as the population of Class 2 cells described there are not Waldeyer cells but local interneurons that do not project through ascending sensory pathways. Indeed, some neurons in lamina I have descending axons (Burton and Loevy, 1976). The concept of 'local interneurons' must therefore be extended to accommodate these descending propriospinal cells.

A promising morphological candidate for the role of the local interneuron in the marginal zone is the 'limiting cell' (Ramón y Cajal, 1890, 1891) also called the 'stalked cell' (Gobel, 1975, 1978). The morphological features of this neuron, intermediate in type between the typical SG neuron and the marginal cell, have been described already. There is some experimental evidence to support this suggestion since Bennett *et al.* (1979) have stained intracellularly a number of limiting cells in the cord of cats with HRP. Six of them were Class 3 cells and another six Class 2 cells. This study both confirms the existence in the marginal zone of neurons showing Class 2 properties and provides support for the suggestion that the limiting cell is also the local interneuron in lamina I showing Class 3 properties.

III. *Physiology of Substantia Gelatinosa Neurons*

During the past four years several research groups have published claims to have recorded single unit activity from the small neurons of the SG. For many years research efforts had been directed towards the physiology of sensory transmission at the dorsal horn level and a great deal of knowledge was gathered on the electrophysiology of dorsal horn neurons and on their interactions. Recordings had also been consistently made from the neurons of lamina I which had proved to be more elusive than those in deeper laminæ. Yet there was a lack of direct information on the properties of the small neurons of the SG. It is therefore not surprising that several research groups have attempted to plug this gap in the knowledge of dorsal horn function.

The present situation can best be described as unsettled. Results reported from different laboratories appear to be in conflict. It is still not clear whether the lack of agreement in results arises only, or mainly, from the use of different types of animal preparation and recording techniques or whether there are other reasons. These differences can be expected to be resolved by work in progress. For the purpose of this review we present all available reports, discuss their points of coincidence and their points of disagreement, but do not attempt to produce a unified view. Appropriate comment on the different techniques and preparations will be made.

A first and important comment which applies to all reports published so far concerns the source of afferent inputs analysed in the experimental studies. Only inputs of cutaneous origin have been studied in any detail so that responses of putative SG neurons have all been interpreted on the basis of integration of skin afferent information. Yet morphological studies have established the SG as the nucleus of reception of most, if not all, unmyelinated afferent fibres and many small myelinated afferent fibres (Aδ) also end in the marginal zone and in lamina II. This indicates that the superficial dorsal horn deals with information coming from many sources and not only from the skin. Many sensory receptors in muscles, joints and other deep structures, as well as most sensory endings in viscera are connected to unmyelinated or small myelinated afferent fibres. Future interpretations of the SG will certainly need to be less biased towards the processing of sensory information from the skin than they are today.

Four research groups have so far published electrophysiological data obtained from the SG. They will be identified geographically in the Discussion. In addition there has been an isolated report by Hentall (1977) which will also be mentioned here.

At Chapel Hill, North Carolina, Perl and co-workers have published two series of reports. In the first series (Kumazawa and Perl, 1976, 1978) extracellular recordings were made in the coccygeal region of the spinal cord of chloralose anæsthetized monkeys. Conventional micropipette electrodes filled with aniline dye were used. No criteria for identification of SG neurons other than location of the recording site within the SG were laid down. In these extracellular studies, units excited by volleys of Aδ afferent fibres and activated either by nocuous mechanical stimulation of the skin or innocuous cooling were mainly found in the marginal zone. In contrast, units exhibiting a strong C-fibre excitation and responses to polymodal nociceptors or C-mechanoreceptors were located in the SG.

A second group of reports from the same laboratory has been published more recently (Light and Perl, 1979*a*, *b*; Light *et al.*, 1979). The sacral regions of decerebrated cats made spinal by cord section were explored by fine microelectrodes (tip diameter 0.05 to 0.7 μm) filled with HRP to attempt intracellular staining of individual neurons. This was successful on 17 occasions. The morphological features and location of the stained neurons served as the criteria for SG neuron identification. However, it is not clear how many of these 17 cells were considered to be SG neurons, since several of the published figures are of typical Waldeyer marginal cells and are so labelled and some confusion thus arises. The previous report of segregation of afferent input according to cell location is confirmed but no relationship could be found between neuronal morphology and physiological response. This is perhaps not surprising in view of the small sample of neurons and their diverse functional properties. Cells excited by nociceptors with Aδ afferent fibres had major dendritic projections in the marginal zone. Cells excited by nociceptors or thermoreceptors with unmyelinated fibres had important dendritic branching in the outer SG. Neurons excited by innocuous mechanical stimulation of the skin had dendritic arborizations in the inner SG when the input came from C-mechanoreceptors or in the outer SG, and lamina III when the afferent drive came from Aδ hair follicle afferents. In addition to this, many neuronal elements in the SG often exhibited a marked, prolonged habituation to innocuous mechanical stimuli, and most of the SG units could be inhibited by cutaneous stimulation.

In 1977, Hentall reported extracellular unit records from the L6 and L7 segments of spinal decerebrate cats. He used platinum-tipped glass-insulated tungsten microelectrodes. Electrical activity was attributed to SG neurons on the basis of electrode tip position (established by depth marking) and novel responses of the units. Thirty-four units were inhibited by innocuous mechanical stimuli with post-excitation on removal of the stimulation. The units showed bursting or continuous background activity and either enhanced firing or no effect after nocuous stimulation.

The Edinburgh research group has published extracellular and intracellular recordings from what are claimed to be SG neurons (Cervero, Ensor, Iggo and Molony, 1977; Cervero, Molony and Iggo, 1977; Cervero *et al.* 1978*b*, 1979*b*, *c*, *d*). Cats anæsthetized with chloralose and paralysed with flaxedil were used and the L6 and L7 segments of the cord were explored with fine glass microelectrodes (Molony, 1978). In an attempt to avoid error, a set of criteria was laid down to differentiate activity recorded from SG neurons from activity generated by other neuronal elements. These criteria were: (i) location of recording sites in the SG (laminæ I and II); (ii) either inflexions in the rising phase of extracellular spikes to identify recordings from or near the neuronal soma, or postsynaptic potentials on intracellular recordings; (iii) short vertical distance over which the unit could be recorded; (iv) antidromic activation and/or postsynaptic effects evoked by stimulation of Lissauer's tract and (v), novel responses to skin stimulation. While these criteria enabled responses to be attributed with confidence to neurons in the SG the criteria were restrictive. There are two major shortcomings: first, Lissauer's tract was stimulated two and three segments away from the recording sites which could not give any information on the segmental circuitry of the SG; secondly, the criterion of excluding recordings similar to those made from larger neurons in the dorsal horn produced a sample of SG neurons which excluded any neurons with characteristics similar to those of neurons in other laminæ. The sample of over 100 neurons was divided into two groups: the majority (>85 per cent) with several common properties were placed in a class called 'inverse', and the remainder were lumped together as class 'heterogeneous'. The emphasis for the 'inverse' SG neurons was given to their conspicuous background activity and to their inhibitory cutaneous fields. Three sub-groups were made: (i) inverse 1 ($\bar{1}$) inhibited by innocuous mechanical stimulation; (ii) inverse 2 ($\bar{2}$) inhibited by nocuous and innocuous stimulation of the skin and (iii), inverse 3 ($\bar{3}$) inhibited only by nocuous stimulation of the skin. Classes $\bar{1}$ and $\bar{3}$ were excited by nocuous and by innocuous stimuli, respectively. The 'heterogeneous' group included neurons showing habituation, long-lasting responses to brief peripheral stimuli, very small cutaneous receptive fields or powerful excitation by nocuous radiant heat applied to the skin. These reports have been followed by a paper describing the identification of the characterized neurons in the SG using intracellular labelling of cells with HRP (Cervero, Molony, Iggo and Steedman, 1980). They were typical central SG neurons.

At University College London, P. D. Wall and his associates have been producing extracellular recordings taken within the superficial dorsal horn (Wall, 1978*b*; Wall *et al.*, 1979; Dubuisson, Fitzgerald and Wall, 1979). Their basic preparations are decerebrate cats and recordings are usually made in the lower lumbar segments through platinum-coated tungsten microelectrodes. Criteria to identify SG neurons include: (i) location of recording sites in the SG by depth gauge (which they consider to be laminæ II and III together); (ii) mis-match in the firing times of neurons in lamina IV and those in II and III; (iii) antidromic and/or postsynaptic responses to microstimulation of the lateral Lissauer's tract and (iv), several electronic technicalities for better isolation of unit recordings such as variable filters or delay lines. There are two major sources of conflict in these criteria. First is the identification of the SG as both laminæ II and III, a view not shared by any of the other groups. Yet, Wall's team found 'no difference in the properties of the units recorded in the two laminæ' (Wall *et al.*, 1979). The second major issue is their method of stimulating Lissauer's tract and the conceptual foundations of their technique. They claim that the lateral Lissauer's tract contains only SG axons. However, morphological studies have shown that the lateral Lissauer's tract contains a substantial proportion of dorsal root afferent fibres (Chung and Coggeshall, 1979). Also, they could only activate their SG neurons antidromically if the stimulating electrode was placed not more than 2.5 mm away from the recording site. Nevertheless, there is abundant morphological evidence that some SG neurons project for distances considerably longer than that (*see* first part of this review). These considerations bring into question the effectiveness of their stimulation technique, since neither afferent fibres in the lateral Lissauer's tract nor intersegmental projecting SG neurons have been reported in their experiments.

Sixty per cent of their units responded only to brush and touch, 20 per cent to brush, touch and pressure and 20 per cent to pressure only. Some also showed one of these three unusual properties; (i) very small (< 2 cm^2) receptive fields; (ii) long-lasting discharges after a single stimulus; (iii) powerful habituation. In a later publication (Dubuisson *et al.*, 1979) the habituation properties of some of their SG units are stressed, together with the description of units having receptive fields whose contours changed spontaneously during exploration (their 'amœboid' receptive fields).

Two papers, published by a research group at NIH, Bethesda, require comment (Bennett *et al.*, 1979; Price *et al.*, 1979). In the first, the cord of cats under sodium pentobarbital anæsthesia was explored with HRP-filled electrodes. Twelve SG neurons of the 'limiting' type were stained intracellularly. Half of them were specific nociceptor-driven neurons (Class 3) and the other half had an input from both low threshold mechanoreceptors and nociceptors (Class 2). The second report from this group (Price *et al.*, 1979) describes results obtained in monkeys under sodium pentobarbital anæsthesia. The lower lumbar segments of the cord were explored with glass-coated tungsten microelectrodes. Attempts were made to record pairs of neurons in the same tract: a dorsal neuron that was a lamina I spino-thalamic tract cell and a second neuron not more than 200 μm deeper. Location of recording sites within the SG by either depth gauge reading or voltage-depth studies was used as the only criterion for concluding that the deeper neuron was an SG cell. They reported a sample of 130 neurons recorded in laminæ I and II. Seven responded only to innocuous mechanical stimulation of the skin; 28 to both nocuous and innocuous stimuli and 95 (73 per cent) to nocuous stimuli only (Class 3 neurons). Thirty-two of these neurons (9 Class 2 and 23 Class 3) were spinothalamic neurons and thus, adopting our classification, Waldeyer (marginal) cells. Price *et al.* (1979) seem to assume that most of the neurons recorded in the outer regions of lamina II are neurons of the 'limiting' type (called 'stalked cells' by them). In addition they described 7 other neurons with 'unusual' properties such as inhibition of spontaneous activity or responses only to C-afferent fibre stimulation.

At first glance, there appears to be little common ground in the results just summarized. It is important to stress that each group has used a different animal preparation and sometimes even different animal species. The recording techniques and type of electrodes used also differed among the various groups. Furthermore, the Chapel Hill and Bethesda groups report samples of neurons containing both marginal and SG neurons. No clear distinctions between the two types of neuron were made in their reports which increases the difficulty of analysing their papers. Nevertheless it is possible to extract from all the published evidence some common features.

One is that SG neurons can be inhibited by cutaneous stimulation, a point which was given prominence in Hentall's and the Edinburgh reports. A second is that all groups described SG neurons showing marked habituation to iterative skin stimuli, a property emphasized in the London reports. Finally, Perl's publications stress the heavy projection of afferent C-fibres to the SG and all groups agree that most SG neurons were powerfully affected by inputs in cutaneous C-fibres.

There are also some important points of disagreement such as the level of background activity of SG neurons and the presence of some cells in the SG and marginal zone excited by fast-conducting afferent fibres from low threshold mechano-receptors. The situation is clearly unresolved and needs a good deal of clarification.

All reports published contain some information regarding the destination and length of the axonal projection of the small SG neurons. Light *et al.* (1979) traced axons in a few of their intracellularly HRP-stained cells. In all cases the axon went towards Lissauer's tract or the dorso-lateral funiculus. Bennet *et al.* (1979) described profuse axonal branching of their limiting (stalked) SG cells in the marginal zone and outer SG. Cervero *et al.* (1979*c*) activated antidromically a few SG neurons (15 per cent) with small myelinated axons from Lissauer's tract two and three segments rostral to the recording sites. Wall *et al.* (1979) found that 50 per cent of their SG cells could be antidromically activated from electrodes placed on Lissauer's tract, with a span of only 2 to 2.5 mm and with conduction velocities typical of C-fibres. These results confirm the projection of some SG neurons through Lissauer's tract and stress the short length of projection of most of their axons. The existence of some neurons in the SG with axons projecting through several segments is also confirmed.

IV. *Descending Influences on Marginal and Substantia Gelatinosa Neurons*

Several morphological studies have described an important projection of descending fibres from supraspinal centres to the maginal zone and the SG. The present state of affairs regarding the supraspinal influences on sensory transmission through the dorsal horn has been reviewed in detail by Fields and Basbaum (1978). Many studies have shown inhibitory effects from brain-stem and telencephalic regions on dorsal horn neurons. Yet, the amount of information available about the effects of the descending systems on marginal and SG neurons is still very small.

The existence of some tonic descending inhibition on nociceptor-driven lamina I neurons was first described by Cervero *et al.* (1976). At the time, all these neurons were presumed to be Waldeyer cells but now it seems that some of them may be SG neurons of the 'limiting' type (*see above*). The amount of tonic inhibition, as revealed by reversible cold block of the spinal cord, was relatively small in comparison to the clear-cut descending tonic inhibition on Class 2 neurons in deeper laminæ (Handwerker, Iggo and Zimmermann, 1975). Nevertheless, a tonic inhibitory effect could be shown to operate on the marginal zone. A similar tonic inhibition on specific nociceptor-driven neurons of the marginal zone was later described in the rat by Necker and Hellon (1978). During reversible spinal block these neurons showed a lowering of their threshold for excitation by nocuous heat.

In the monkey, Willis, Haber and Martin (1977) reported that spinothalamic tract neurons located in lamina I (presumably Waldeyer cells) and responding only to noxious stimuli could be powerfully inhibited by electrical stimulation of the raphé nuclei, particularly the nucleus raphé magnus. This inhibition was abolished by section of the dorso-lateral funiculi, therefore implying that the descending inhibitory pathway runs in that part of the white matter. Other kinds of inhibitory influences on dorsal horn neurons, such as the inhibition of supraspinal origin triggered by nocuous stimulation of areas of the body remote from the receptive fields of the neurons, (diffuse noxious inhibitory control, or DNIC) do not seem to affect the nociceptor-driven neurons of lamina I (Le Bars, Dickenson and Besson, 1979). In summary, it is clear that some forms of tonic and phasic inhibition operate on the cells of the marginal zone. As with other dorsal horn neurons the inhibitory systems are not single nor are all possible systems operative in this area.

Very little is known of the effects of descending pathways on SG neurons. Cervero *et al.* (1979*d*) have reported that their 'inverse' SG neurons seem not to be under sustained tonic influences from supraspinal centres. Nevertheless, they were able to inhibit most SG neurons by short trains of stimuli applied to the ipsilateral dorsolateral funiculus several segments rostral to the recording site, thus suggesting the existence of a system with possible phasic actions. This is clearly an aspect of the physiology of the SG that needs extensive examination, not least because of the powerful modulating effects of supraspinal mechanisms acting elsewhere in the dorsal horn.

V. *Histochemistry and Pharmacology of the Substantia Gelatinosa*

A number of biochemical, histochemical and pharmacological techniques have been used in an attempt to identify the chemicals involved in the function of the SG. Techniques are diverse and no mention of their details will be made here. Nevertheless, data relevant to the understanding of the SG circuitry and obtained by the application of such methods must obviously be included in any attempt to review current views on the functional role of the SG.

Refined histochemical techniques have revealed a long list of substances present in different areas of the central nervous system to which transmitter or other functional roles have been attributed. Most of the substances are peptides, and many are also found in other parts of the body, particularly in the gut (Hökfelt, Johansson, Ljungdahl, Lundberg and Schultzberg, 1980). Nearly all of them have been shown to be present in the SG, either specifically (and in relatively high concentrations) or as part of a more diffuse distribution that extends all over the spinal cord grey matter.

In many cases their presence in the SG is all that is known about them. This group of substances will only be mentioned here. Other peptides have been studied more extensively and consequently more detailed descriptions will be presented.

Angiotensin II has been shown to be present in SG cells and in nerve terminals of the SG (Fuxe, Ganten, Hökfelt and Bolme, 1976; Changaris, Keil and Severs, 1978).

These observations, based on immunofluorescence techniques have been questioned by other investigators (Reid, 1979). Cholecystokinin (CCK) appears to be distributed in nerve terminals in the SG but not in the somata of the SG cells (Larsson and Rehfeld, 1979). Similar distributions have been described for vasoactive intestinal peptide (VIP) (Loren, Emson, Fahrenkrug, Björklund, Alumets, Hakanson and Sundler, 1979), neurophysin I and oxytocin; the latter two being present in high concentrations inside the endings of descending fibres of the dorso-lateral funiculus terminating in the marginal zone (Swanson and McKellar, 1979).

A very dense network of neurotensin-containing terminals has been described in the SG (Uhl, Kuhar and Snyder, 1977). Reaction product was only present in neural elements that looked like nerve terminals and was unaffected by dorsal root section, thus suggesting that neurotensin is present in the endings of descending fibres to the SG. The presence of monoaminergic pathways ending in the SG and marginal zone has been indicated in the preceding pages. Monoamine containing endings have been identified in the SG of the rat (Carlsson, Falck, Fuxe and Hillarp, 1964; Dahlström and Fuxe, 1964) and the monkey (Crutcher and Bingham, 1978). GABA-containing endings have also been described in the SG, and identified as axonal endings of SG neurons. These endings were found presynaptic to other SG neurons, to dendrites of neurons in lamina IV or to primary afferent endings (glomeruli) (Barber, Vaughn, Saito, McLaughlin and Roberts, 1978).

There is a group of substances which have been found in great quantities in the SG but that disappear after dorsal rhizotomy. These chemicals (acid phosphatase, somatostatin and substance P) are thought to be present in the central endings of the unmyelinated primary afferent fibres, which would explain their selective presence in the SG and their susceptibility to dorsal root section. Fluoride-resistant acid phosphatase (FRAP) also called extra-lysosomal acid phosphatase (EXAP) is present in the central ending of the glomeruli in the SG (Knyihar and Csillik, 1976). Its presence is related to the content of substance P. Acid phosphatase deposits in the SG are depleted by the administration of capsaicin (Jancsó and Knyihar, 1975), a chemical known to render animals insensitive to chemical painful stimuli and to block the thermoregulatory responses to the treated animals (Jancsó, Kiraly and Jancsó-Gábor, 1978). Another substance shown to be present in the central endings of unmyelinated afferent fibres in the SG is somatostatin (Hökfelt, Elde, Johansson, Luft, Nilsson and Arimura, 1976). Like substance P, somatsostatin is distributed along the length of the fibre and deposits occur at both ends (receptor and central end). Apparently the population of C-fibres containing somatostatin is different from that containing substance P (Hökfelt *et al.*, 1976). It would be interesting to know whether this segregation of C-fibre populations based on their histochemical properties has a parallel in their functional responses.

The last and best-known substance present in the central endings of afferent C-fibres is substance P (SP). It was proposed as a neurotransmitter for C-fibres by Lembeck in 1953; a view which has gained many adherents (Henry, 1976; Otsuka and Konishi, 1976; Zieglgänsberger and Tulloch, 1979). SP is present in the central endings of small fibres in the SG and in fibres running along Lissauer's tract (Hökfelt, Kellerth, Nilsson and Pernon, 1975 and Hökfelt *et al.* 1976). Not all of it is of dorsal root origin; a small amount of SP-containing terminals and cells survive dorsal rhizotomy (Barber, Slemmon, Salvaterra, Roberts and Leeman, 1979). The SP content of the dorsal horn is depleted by capsaicin treatment (Jessell, Iversen and Cuello, 1978) which causes it to be released from the nerves (Theriault, Otsuka and Jessell, 1979). Parallel to SP release, capsaicin induces powerful thermal analgesia (Yaksh, Farb, Leeman and Jessell, 1979). All these observations are consistent with the view that SP has a transmitter function in the nociceptive pathway, particularly at the first synapse of C-fibres within the SG.

A point that needs consideration is the relationship between the endings containing SP and the opiate receptors described in the SG. Autoradiographic studies have shown a high density of opiate receptors in the SG (Pert, Kuhar and Snyder, 1975; Atweh and Kuhar, 1977). On the other hand Hökfelt, Ljungdahl, Terenius, Elde and Nilsson (1977) described the presence of met-enkephalin within the cell bodies of many neurons in the SG and marginal zone. The contents of met-enkephalin in the SG are not affected by dorsal root section, whereas the number of opiate receptors is dramatically reduced after deafferentation (La Motte, Pert and Snyder, 1976). The presence of exogenous opiates during the incubation of an *in vitro* preparation of slices of rat trigeminal nucleus suppresses the stimulus-evoked release of SP (Jessell and Iversen, 1977). In an attempt to integrate all these observations Jessell and Iversen proposed the following model: (i) SP is the neurotransmitter released by C-fibres during noxious stimulation; (ii) C-fibres make synaptic contacts in the SG with dorsal dendrites of deeper neurons related to sensory ascending pathways, such as the spinothalamic tract; (iii) SP-containing endings of C-fibres have opiate receptors in their membranes; (iv) enkephalin-containing neurons in the SG modulate transmission of nociceptive information through the SG by presynaptically inhibiting transmission through the 'SP-ergic' synapse between afferent C-fibres and spinothalamic tract neurons.

This model is an ingenious attempt at unifying neurochemical and neurophysiological data, but on close examination it is clear that it contains many oversimplifications, nor does later evidence fit into the proposed mechanism. The major shortcoming of the model is the assumption that the three main neuronal elements involved (afferent C-fibres, SG neurons and neurons in lamina IV) are pools of uniformly-behaving cells. However, the population of C afferent fibres contains many of non-nociceptive nature (Iggo, 1959, 1960, 1969) particularly mechanoreceptors and both cold and warm thermoreceptors (*see* Burgess and Perl, 1973). Similarly, recent studies on SG neurons have shown that they do not respond as a unimodal population to afferent inputs, which makes unlikely the postulated unique action of these cells in Jessell and Iversen's model. Also, the number of enkephalin-containing neurons in the SG is less than first thought, and many Waldeyer cells in lamina I contain enkephalin (A. I. Basbaum, personal communication), which clearly points to the need to revise ideas in respect of the functional significance of opiate receptors and endogenous opioids in the SG. A further piece of evidence against the suggested model has been provided by Duggan, Griersmith, Headley and Hall (1979), who found that ionophoretic application of SP in the SG has no effect on the responses of neurons in lamina IV to noxious stimuli. These observations seriously question the role attributed to SP as a neurotransmitter in the nociceptive pathway.

In this line of pharmacological research it is relevant to mention the effects of ionophoretically applied substances reported on the response properties of nociceptor-driven lamina I neurons and on the functions of SG cells. The effects of a number of chemicals on the responses of Class 3 lamina I neurons have been analysed (Randić and Yu, 1976; Randić and Miletić, 1977; Miletić and Randić, 1979). Inhibition of their responses to noxious stimulation was achieved by ionophoretic application of serotonin (5-HT). Neurotensin, bradykinin and, in particular, SP enhanced the excitatory responses. Using a different approach, Duggan's group have studied the effects of locally applied substances in the SG on transmission of noxious information through the dorsal horn (Duggan, Hall and Headley, 1976, 1977; Duggan *et al.*, 1979; Headley, Duggan and Griersmith, 1978). The chemicals were ejected ionophoretically from a micropipette placed in the SG, while the electrical activity of neurons located deeper in the dorsal horn (laminæ IV and V) was recorded. Selective depression of the nocuous responses of lamina IV Class 2 neurons followed met-enkephalin injection in the SG. A similar effect was produced by noradrenaline whereas 5-HT was less selective in its inhibitory actions. In contrast, the ejection of SP into the SG did not produce any effect on the activity of deeper dorsal horn neurons.

It is not easy to extract conclusions from the histochemical or pharmacological studies. The role of SP as a neurotransmitter for C-fibres is far from being established and in any case it remains to be discovered whether SP is present, or indeed has unique functions, in all functional types of primary afferent C-fibres. Enkephalins are present in the SG, as are opiate receptors. Their functional role is still open to question. Other proposals such as the inhibitory effects of 5-HT on dorsal horn neurons, including marginal cells, seem to be more positively established.

VI. *Current Opinions on the Functional Role of the Substantia Gelatinosa*

Recent publications of functional responses of neurons in the SG permit a fresh conceptual approach to the functional role of the SG. It is now possible to speculate on the functions of the superficial dorsal horn from the vantage point of knowledge of the electrophysiological responses of marginal and SG neurons. Two basic interpretations of the functions of the SG have emerged from the publications reporting single unit recordings. Some authors see the SG as a receiving station and relay nucleus for primary afferent fibres whereas others have elaborated more complex interpretations of the SG in respect to its role as a nucleus of interaction and modulation of cutaneous sensory information. These two views are by no means exclusive and in many respects may be considered complementary, if not almost identical. Nevertheless they will be presented separately.

The idea of the SG being a relay nucleus for primary afferent fibres originated from the work of Perl's group (Kumazawa and Perl, 1978; Light *et al.*, 1979), which emphasized the close correlation between the anatomical distribution of dorsal root afferent fibres in the superficial layers of the dorsal horn and the functional properties of their SG neurons. They advance the idea that some marginal and SG neurons transmit information about nocuous stimulation. They also describe neurons in the same region driven by small Aδ and C afferent fibres responding to innocuous thermal or mechanical stimuli, although these show rather extensive excitatory and inhibitory convergence. They conclude that the marginal zone and the SG are areas of relay of small primary afferent fibres which subserve a variety of functions, such as integration of sensory information or interaction of segmental reflexes, and that a single unified theory of their function role is untenable. This view is supported and extended by Price *et al.* (1979), who report that marginal and SG neurons are driven not only by small dorsal root fibres but also by fast-conducting large primary afferents. Since the anatomical studies have clearly shown that large afferents do not end in the more superficial areas of the dorsal horn, they conclude that some SG neurons fulfil the role of relaying these inputs to those marginal cells that have Class 2 properties and project through the spinothalamic tract. They suggest that SG neurons of the 'central' type may convey innocuous inputs whereas those of the 'limiting' (or 'stalked') type relay nocuous information. This implies that some SG neurons must be of an excitatory nature, an assumption unsupported by experimental evidence. This assumption does not rule out the role of SG neurons as inhibitory interneurons which will, according to Price *et al.* (1979), help to sharpen the excitatory inputs by adding surrounding inhibition.

Wall *et al.* (1979) have considered the functions of SG neurons at a higher level of conceptual interpretation. In a review, Wall (1978*a*) has re-examined and re-stated the basic theoretical principles of the 'gate control' theory and removed the emphasis from the detailed mechanisms. Nevertheless, 'gating' properties are still attributed to the SG as a whole (Wall, 1978*a*), although it appears very difficult to attribute any 'gating' function to the kinds of SG neurons they find (Wall *et al.*, 1979). There seems to be a gap between the experimental evidence produced and the wide conceptual implications derived from it. It is not clear how neurons showing habituation, 'amœboid' receptive fields, long-lasting responses after short stimuli or small receptive fields can act on other neuronal elements in order to 'gate' the traffic of sensory information.

A more detailed model of functional interaction between SG neurons and other dorsal horn cells has been produced by Cervero and Iggo (1978). Their diagram is a mixture of experimental evidence and speculation. They propose a model of 'reciprocal sensory interaction' in the dorsal horn by which the afferent input from mechanoreceptors and nociceptors interact with SG and dorsal horn neurons. SG neurons are proposed to act as inhibitory interneurons on larger dorsal horn neurons. An inverse correlation between the excitatory drives of dorsal horn neurons (Classes 1, 2 and 3 cells) and the 'inverse' responses of their SG neurons is postulated and appropriate inhibitory links between the two sets of cells are proposed. Their concept is based on the Sherringtonian principle of reciprocal inhibition of segmental reflexes by which the activation of a reflex arc leads to the inhibition of the antagonist muscles. In Cervero and Iggo's model the activation of one sensory channel (either mechanoreceptor or nociceptor) results in the inhibition of the other sensory transmission systems.

A central assumption in the model of 'reciprocal interaction' and indeed in many of the functional interpretations of the SG, is that SG neurons are basically inhibitory interneurons. The existence of SG neurons having excitatory properties, on the other hand, is fundamental in Price *et al.*'s (1979) interpretations of the SG and has not been denied by other authors, but the general tone of interpretation of the SG is that many of its neurons are inhibitory in their action. There is no direct evidence to support this assumption, but morphological interpretations (Kerr, 1975) and several indirect analyses of the functions of the SG are consistent with the idea that they are inhibitory interneurons (Denny-Brown *et al.*, 1973; Duggan *et al.*, 1977; Wall and Yaksh, 1978).

A final point of note can be made on the possible role of SG neurons in presynaptic inhibition. Wall (1962) presented experimental evidence linking SG neurons with the generators of dorsal root potentials, and reported that the integrity of Lissauer's tract was essential for the intersegmental spread of dorsal root potentials. As mentioned before, this was of relevance in the presynaptic role attributed to SG neurons in the 'gate' model (Melzack and Wall, 1965). An attempt by Cervero *et al.* (1978*a*) to reproduce these results failed to show dependence of dorsal root potentials on the integrity of Lissauer's tract. This observation and the wealth of morphological data regarding the great numbers of axo-dendritic and axo-somatic synapses in the SG seem to indicate that many effects of SG neurons can clearly be explained in terms of postsynaptic rather than presynaptic influences. Nevertheless, the mechanisms of presynaptic inhibition are still obscure and a role for SG neurons in their generation remains a possibility.

CONCLUDING REMARKS

The experimental evidence leads us to conclude that the SG is neither structurally nor functionally homogeneous. For many years, investigators have been misled by the apparent uniformity of the structure of the SG and its differentiation from the rest of the spinal cord grey matter. This fact accounts for the separation of the SG from the rest of the dorsal horn by Rolando more than one-hundred and fifty years ago and the special treatment that the SG received from the morphologists at the turn of the century. It has to be recognized that the SG offered the double attraction of being an enigmatic structure in itself and owing part of its mystery to the fact that it was the nucleus of reception of unmyelinated afferent fibres. It was very tempting to create a separate functional entity by linking this structure in the cord, full of very small neurons and intricate connections, with its principal input, namely the large numbers of unmyelinated afferent fibres of which very little was known, except that they were considered to be 'pain' fibres.

What then are the functions that the SG may subserve? Some insights can be gained by analysing what is now known about its structure and the functional responses of its component cells. The SG receives the bulk of the C-fibre afferent projection to the cord as well as many small myelinated afferent fibres. Its cell density is very high; in proportion to the larger dorsal horn neurons estimated ratios run as high as 100 : 1, and these are probably conservative. SG cells are profusely interconnected as well as ending on other dorsal horn neurons. A few project to supraspinal regions. Connections are generally short and in many cases axons of SG cells span only one segment, although intersegmental connections may extend as far as 4 or 5 segments. Functional analysis of the SG has confirmed the anatomical observations regarding afferent fibre distribution and has also shown that some SG neurons respond to cutaneous inputs in a manner different from other dorsal horn cells.

The first conclusion is that the SG is clearly in a privileged position to act as a relay station between small afferent fibres (Aδ and C) and dorsal horn neurons. This function carries the corollary that some SG cells may also be involved in the integrative processes consistent with a relay action, such as lateral or surrounding inhibitory interaction between afferent inputs and in a sustaining, reverberatory role. If this secondary function is elaborated further, then part of the cell population of the SG may be implicated in particular integratory mechanisms. Their relation with the C-fibre projection points to nociception as a major candidate. The presence of chemicals such as enkephalin or SP adds support to this view. Important as it may be, nociception is not the only function with which the SG is concerned. The relay interpretation involves processes such as segmental or propriospinal reflexes, conveying of the C-input from thermo- and mechanoreceptors to projection pathways and other functions outside the specific mechanisms related to nociception.

If functions are diverse and the only common ground is a vague reference to relay function, is it then useful or necessary to maintain the concept of the SG? After all, there are many interneurons in deeper parts of the dorsal horn or in the ventral horn subserving relay functions. Are there any properties, morphological or functional that make the SG unique? These questions enhance the problem that is probably at the heart of all discussions on the SG: what exactly is the SG? If the definition of SG is taken from its original description, then this 'substance' is an area of the grey matter of the spinal cord and includes all cellular elements within its borders. This concept of the SG is functionally meaningless since it will imply the existence of rigid functional separation between the inside and the outside of the SG. Furthermore, will the marginal cells then be included in the SG?

It is obvious that the 'substantia gelatinosa' has no real meaning as a functional entity. The term should be reserved to describe an area of the grey matter in topographical terms. For the purposes of physiology the questions should be directed to cell types of the SG rather than to the SG as a whole.

Taking this line we can recognize at least three functional entities in the SG: the marginal cells; the small (or 'central') SG cells and the 'limiting' SG neurons. The marginal cells are closer to other types of projecting neuron in the deeper dorsal horn than to other neurons of the SG. They are a group of cells, functionally allied to other spinal cord projecting neurons but located where their input is, namely, in that place of the dorsal horn rich in Aδ and C afferent fibres. 'Limiting' cells are, accepting the so far scarce evidence, indistinguishable from other interneurons of the dorsal horn. In this respect it may prove useful to look at the ventral border of the SG, that is lamina III, and consider this region similar to the dorsal border. It contains some large projecting neurons and many smaller interneurons. In between these two borders lie the mass of 'central' SG neurons, the only ones that may have unique functional properties.

The 'SG' is a purely morphological concept. Its use as a functional term is both misleading and meaningless. Within the SG are neurons which probably subserve very specialized relay functions including integration and interaction between sensory channels. Ventral and dorsal to the SG there are areas containing cells related to more general functions of conveying sensory information or linking reflex pathways.

A great deal of recent work on the anatomy and physiology of the SG has contributed to a better knowledge of this area and of the general functions of the dorsal horn, and has thus succeeded in removing at least some of the mystery that had been veiling the functional interpretations of this region of the spinal cord.

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COMPARISON OF THE EFFECTS OF TRANSCORTICAL AND TRANSCALLOSAL REMOVAL OF INTRAVENTRICULAR TUMOURS

by GINA GEFFEN, ANTHONY WALSH, DONALD SIMPSON
and MALCOLM JEEVES

(*From the Centre for Neurosciences, The Flinders University of South Australia, the Department of Neurosurgery, Adelaide Children's Hospital, South Australia and the Psychological Laboratory, University of St. Andrews, Fife, Scotland*)

INTRODUCTION

THERE is substantial evidence from the study of patients with sections of their cerebral commissures that the fibre tracts of the corpus callosum and anterior commissure have an essential role in the transfer of sensory information from one cerebral hemisphere to the other (Gazzaniga, 1970; Sperry, 1970). Moreover, the close relatives of such patients reported that they have observed post-operative, recent memory deficits that have persisted for several years (Zaidel and Sperry, 1974). In 8 patients with complete section of all forebrain commissures, and 2 patients with a similar section but with the splenium spared, Zaidel and Sperry (1974) reported that there was a significantly lower score on the Wechsler Memory Scale (WMS) than the Wechsler Adult Intelligence Scale (WAIS). The WAIS-WMS correlation in normal subjects was 0.83 (Fields, 1971). Deficits were also demonstrated on other standardized memory tests. They concluded that 'the frontal two-thirds of the callosum . . . seems to be implicated as being involved in mnestic functions'.

Two recent case reports that examined the cognitive effects of sectioning the callosal fibres appear to be contradictory. Dimond, Scammell, Brouwers and Weeks (1977) concluded that the procedure (section of the trunk of the callosum) to remove an angioma from the left lateral ventricle resulted in aphasia, neglect, extensive somatic disconnection and 'autopragmatic amnesia'. On the other hand, a remarkable recovery of various cognitive functions following total section of the corpus callosum (sparing the anterior commissure) in order to relieve epilepsy has been reported (LeDoux, Risse, Springer, Wilson and Gazzaniga, 1977).

The above studies have specifically implicated the great cerebral commissures (but not the splenium) in recent memory functions. The present report compares the cognitive functioning of 2 patients with partial section of the callosum to relieve intraventricular tumours, with that of 2 patients who underwent cortical sections during operations done to relieve similar conditions. The same tests were given to a patient with agenesis of the corpus callosum to test whether this different ætiology involving the same structure has similar consequences.

CASE REPORTS

Table 1 summarizes the details of all patients.

TABLE 1. PATIENT'S AGE, SEX, DIAGNOSIS AND OPERATIVE APPROACH

Patient	*Sex*	*Age (yrs) (last test)*	*Diagnosis*	*Operation*
W.F.	F	22	Third ventricle cyst	Transcallosal aged 14 yrs Right hemisphere retracted Bilateral fornix transection
G.O.	M	69	Third ventricle cyst	Transcallosal aged 62 yrs Right hemisphere retracted Minor right fornix damage
L.K.	F	26	Left lateral intraventricular meningioma	Transcortical aged 23 yrs Left middle temporal gyrus approach
J.H.	F	29	Third ventricle cyst	Transcortical aged 28 yrs Right frontal approach
P.H.	M	26	Congenital acallosal	No operation

Transcallosal

The histories of Cases 1, W.F., and 2, G.O., have previously been reported (Jeeves, Simpson and Geffen, 1979), and are summarized here.

Case 1. W.F., aged 14 years, had complained of headache over the last two months, with increasing lethargy. On the day of her admission, she passed into a state of rapidly deepening coma. While in hospital, she ceased to breathe and her pupils became fixed. Ventricular drainage was instituted, and ventriculography with air and sodium iophendylate was performed. This investigation demonstrated what appeared to be a midline tumour in the septum pellucidum.

An attempt was made to perform a ventriculocisternal shunt, but in the course of this, the 'tumour' was tapped, and a certain amount of dark fluid containing cholesterol was obtained.

After these investigations, she exhibited a left facial and brachial hemiparesis with some dyskinesia. There was marked impairment of recent memory and she was apathetic, confused and incontinent.

At operation (October 15, 1971), the right frontal lobe was exposed through a small craniotomy. The frontal lobe was retracted after division of one large vein. This permitted exposure of the corpus callosum; the pericallosal arteries were retracted to the left and the body of the corpus callosum was incised posterior to the genu, which was preserved. The length of the incision was probably less than 30 mm. When this was done, the lateral ventricle could be explored, and a greyish-green cyst was seen occupying the foramen of Monro. It contained yellow fluid and also a certain amount of necrotic material. To expose it fully, it was necessary to divide the pillars of the fornix, and when this was done it was possible to strip the tumour away from the tela choroidea.

This operation was well tolerated. The left facial and brachial paresis rapidly recovered, as did a post-operative complaint of abnormal thirst, but for some time there was marked impairment of recent memory. Histologically, the cyst was originally considered to be an epidermoid, but further examination led to reclassification as a colloid (so-called paraphyseal) cyst.

After discharge, there was further clinical improvement, and the girl was able to complete a normal education. Five years after the operation she is very well and has no neurological symptoms except forgetfulness over minor matters; she finds a diary helpful. She is attending a teachers' training college and is expected to qualify as a primary school teacher.

Case 2. G.O., aged 64 years, complained of episodes of depression, impaired mental concentration, and sudden attacks of weakness in the legs which caused falling without warning. Examination showed him to be orientated in time and place, but with a significant defect in recent memory. There was symmetrical tendon hyperreflexia but plantar responses were flexor. The optic fundi were normal.

Carotid angiography showed evidence of hydrocephalus, and a lumbar pneumoencephalogram showed a mass 20 mm in diameter occupying the anterior third ventricle. Filling of the lateral ventricles was incomplete.

A colloid cyst of the third ventricle was diagnosed. At operation on March 10, 1972 the right frontal lobe was exposed through a small bone flap. It was retracted from the falx and, after the sacrifice of one small bridging vein, the corpus callosum was exposed for a distance of about 30 mm. After separation of the two anterior cerebral arteries, the corpus callosum was incised and the dilated lateral ventricle was opened. A cyst could be seen occupying the foramen of Monro on the right side, with a large vein—presumably the septal vein—running over its surface. It was necessary to incise white matter (probably thinned-out fornix) to expose the posterior surface of the cyst, which was tough and rubbery; it contained semi-solid material and, when this was evacuated, the cyst collapsed and could easily be detached from its vascular adhesions. Removal was complete, with no damage to neurological structures other than the corpus callosum itself and a portion of the right fornix.

This operation was well tolerated, and the patient showed no obvious ill-effects during his convalescence. His subsequent course has, however, been less satisfactory. Some eighteen months after this operation, he was readmitted in a depressed state with evidence of impaired recent memory. Further lumbar pneumoencephalography was performed, demonstrating considerable ventricular dilation, and a CSF isotope transport study suggested delay in CSF absorption externally. A ventriculo-atrial shunt was performed, and this, together with appropriate psychiatric treatment, somewhat improved his condition. Five years after the original operation, depression no longer appears to be a significant problem, but he remains diffident, reticent and very much dependent on his wife. He now denies any memory defect, and his wife endorses this. When last seen he accurately recalled an address and the name of a flower after an interval of five minutes.

W.F. was given further tests of memory and disconnection on three occasions in the University laboratories. No intellectual and memory assessment had previously been carried out on G.O. The present report contains results of intelligence, memory and disconnection testing in three sessions in G.O.'s home. Figs. 1A and C indicate the approximate location of cysts and operative approaches for W.F. and G.O., respectively.

Transcortical

Case 3. L.K., an enrolled nurse, was admitted to the Royal Adelaide Hospital on April 1, 1976 at the age of 23 years, after several episodes of acute bifrontal and occipital headaches associated with vomiting. These episodes increased in frequency and were finally associated with dressing dyspraxia and dysphasia. Examination on admission showed no localizing neurological signs but she had definite bilateral papillœdema and also small, mainly right-sided, retinal hæmorrhages. Her visual acuity was worse in the right than the left visual field. The field of vision was full to confrontation. EEG examination showed markedly abnormal activity of a general nature mainly on the left posterior side. Skull radiographs, brain scan and left carotid and vertebral angiograms indicated a meningioma in the left lateral ventricle. Behavioural observations showed normal speech and intelligence and a reasonably good performance on memory testing. There was no anomia.

On April 9, 1976 a left lateral craniotomy was performed with the removal of a tumour from within the left lateral ventricle. The operation was long (five and a half hours), and was performed through a left lateral bone flap. The middle temporal gyrus appeared broadened and the tumour (5.5 cm in diameter) was located 3 cm under the anterior part of this gyrus by a brain needle. The incision in the temporal lobe was about 4 cm long and a typical lobulated meningioma was encountered which occupied the vestibule of the lateral ventricle and extended into the body of the ventricle. The dissection required to define the tumour involved the anterior part of the temporal horn of the ventricle

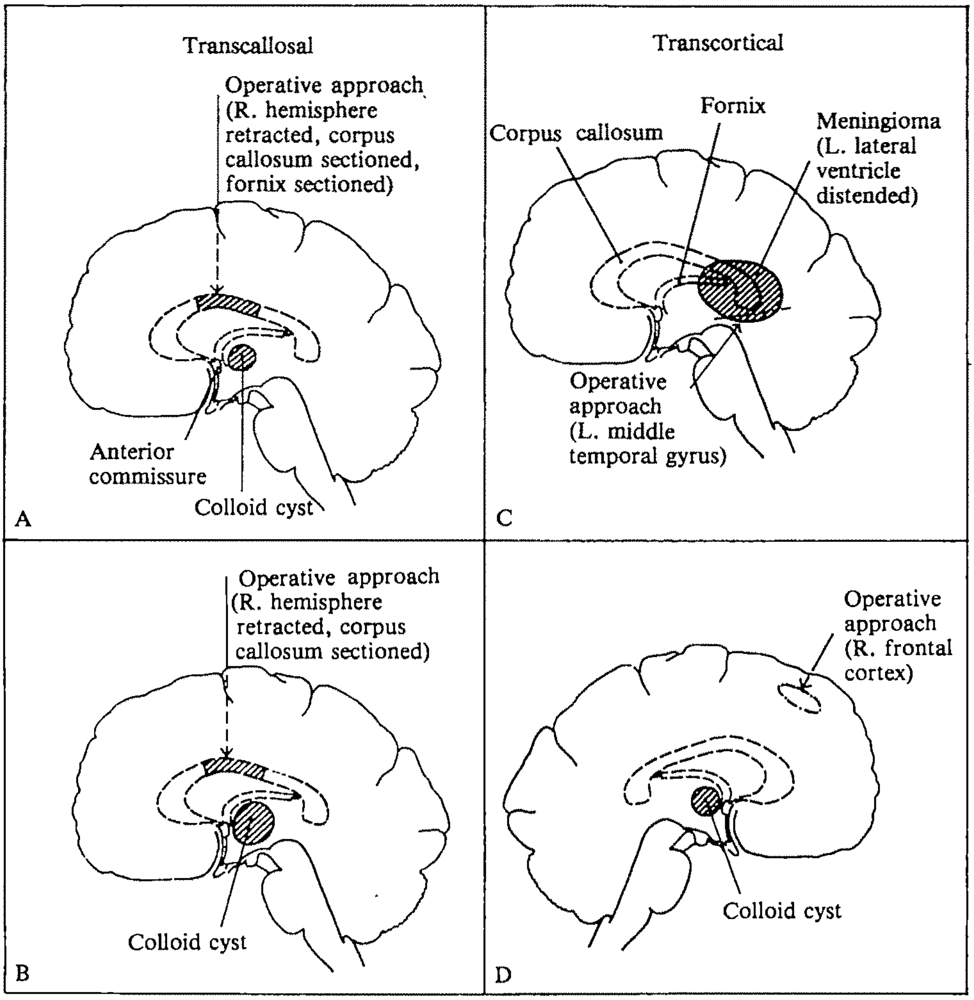
Transcallosal
Operative approach (R. hemisphere retracted, corpus callosum sectioned, fornix sectioned)
Anterior commissure
Colloid cyst
A
Transcortical
Corpus callosum
Fornix
Meningioma (L. lateral ventricle distended)
Operative approach (L. middle temporal gyrus)
C
Operative approach (R. hemisphere retracted, corpus callosum sectioned)
Colloid cyst
B
Operative approach (R. frontal cortex)
Colloid cyst
D

FIG. 1. Diagrams showing approximate location of cysts/tumours and the operative approaches relative to the ventricular system and corpus callosum in A, W.F., B, L.K., C, G.O., D, J.H.

and the choroidal plexus, and the clipping and transection of the anterior choroidal artery. The superior aspect was seen to be embedded in white matter and was carefully defined and totally removed. A large cavity was left which was confluent with the lateral ventricle. The operation was well tolerated. It was noted there was no post-operative hemiparesis and there was good comprehension of speech; nominal ability, however, was severely impaired and there was a right-sided hemianopia.

An EEG recording since the operation (October 24, 1977) showed an improvement over her pre-operative record but the left temporo-parietal area still showed abnormal activity with some sharp waves. Her speech and dyslexia improved with speech therapy, and now she finds problems only when reading books to her child and when she is tired. She has returned to work and is a part-time nurse on night duty in a general hospital. She is unable to drive because of her complete right homonymous hemianopia.

She was co-operative during the three testing sessions in the laboratory. The instructions for the Benton Visual Retention Test were modified to remind her to scan her missing right visual field (*see* fig. 1B for location of tumour and operative approach).

Case 4. J.H. had been a stenographer for ten years. She presented on October 2, 1977 (aged 28 years) with a two-day history of severe frontal headaches with increasing drowsiness. She was semi-conscious on admission and does not recall her illness. She responded only to pain and occasionally to verbal stimuli. Her eye movements were independent, her pupils small but reacting. The fundi were thought to show early papillœdema.

Before operation her conscious state deteriorated. Her right pupil was larger than the left and pupil reaction was slow. There was marked bilateral hypertonia with bilateral cog-wheeling of the arms and bilateral ankle clonus. Radiographs of the skull and computer tomography showed a probable colloid cyst at the third ventricle with gross obstructive hydrocephalus. Bilateral ventricular drainage was performed but this brought no improvement and a craniotomy and incision of the colloid cyst was performed.

The procedure was carried out *via* a right frontal bone flap. A cone of frontal lobe was excised (2 to 2.5 cm in diameter) and the right lateral ventricle was entered. From here the septum pellucidum was fenestrated with partial emptying of the left lateral ventricle. The septum pellucidum was then pushed medially and the lateral wall of the ventricle laterally to explore the foramen of Monro. Here a thin-walled greenish cyst was encountered occupying the foramen and attached to the choroid plexus. The fornix looked stretched. The cyst was emptied and separated and delivered into the lateral ventricle. The right fornix seemed rather bruised by the procedure. The attachment to the choroid plexus was coagulated before separation. The ventricular drain was reinserted.

Her progress was satisfactory although she remained confused and disinterested, and slept excessively. She had almost total bilateral ptosis and marked ophthalmoplegia. An EEG recorded on November 15, 1977 was abnormal with generalized right frontal disturbances; however, no epileptic activity was seen. She was discharged on November 28, 1977.

Psychological testing just before her discharge (November 25, 1977) included the WAIS. Her scores were very low with her over-all IQ in the bottom 10 per cent of the population distribution; her verbal IQ, however, was in the normal range with performance IQ in the bottom 2.2 per cent of the population distribution indicating greater damage to the right than the left hemisphere. Her memory for instructions of the test and of her surroundings was poor.

She was co-operative during testing. However she worried about her performance and required continual reassurance. She was most concerned about her memory. In casual conversation she repeated the same question three or four times apparently without awareness of doing so. She also forgot her jumper even when she complained of the cold, but when given the WAIS (July 31, 1978) she remembered having been given the test previously. At the last test session, which was in her home (August 30, 1978) she appeared very much improved in her personal control and her ability to cope with the testing. A diagram showing the approximate location of the cyst and operative approach is shown in fig. 1D.

Case 5. P.H. was referred in 1960 (aged 6 years) for neurological testing. Plain skull x-rays and ventriculography showed the shape of the ventricles and their positions to be abnormal, with the diagnostic conclusion that there was agenesis of the corpus callosum which appeared to be total. He was noted to be right-handed.

P.H. was given a series of psychological tests in 1960 (Jeeves, 1965). The WISC showed a full scale IQ of 75 with a discrepancy of 13 points in favour of the verbal score over the performance score. His bimanual co-ordination was poor and he showed restricted transfer of learning across hands but his cross-localization of tactile information was normal. He was again tested in 1977 (Jeeves, 1978). P.H. (now 24-years-old) enjoyed being tested. He remembered all the persons who had previously tested him and even described some of the tests he had taken when 6 years of age.

PSYCHOLOGICAL TESTING

The standardized tests included the WAIS and WMS. The WMS consists of 7 sub-tests: the first 2 involve details such as the patient's birth date, age, name of the Prime Minister (Current Information) and questions about the day, month and place (Orientation). The third sub-test involves saying the alphabet as quickly as possible, counting backwards and counting in threes or fours (Mental Control). Thus the first three sub-tests are not memory tests *per se* but are a useful standard measure of whether the patient is confused. In the amnesic syndrome, the separate sub-tests sensitive to deficits (of recent memory) are associative learning, visual reproduction and story passages, in that order (Walsh, 1978). In contrast, Digit Span (testing immediate memory) appears normal.

Although the validity of the WMS as a test of memory ability has been questioned (Eysenck and Halstead, 1945; Parker, 1957), 'the high correlation (of the WAIS and WMS) in normal subjects makes a large IQ-MQ difference very suggestive of a memory disorder' (Walsh, 1978, p. 317), and the same tests as those used by Zaidel and Sperry (1974) had to be administered.

The revised Benton Visual Retention Test (BVRT, Benton, 1955) was also used by Zaidel and Sperry. It consists of 10 designs, each of which is shown to the patient for 10 s followed by the patient reproducing the design from memory. Form C was used in this way to test immediate recall (Administration A) and represents an extension of the visual reproduction sub-test of the WMS. Delayed recall (not tested by Zaidel and Sperry) was investigated by inserting a 15-s delay after presentation before allowing the patient to reproduce the design. Form D (a different set of designs) was used for this.

Cumulative learning was tested using Hebb's digit-sequences task (Baddeley and Warrington, 1970). Twenty-four trials of sequences of random digits, each sequence one digit longer than the patient's memory span, were spoken at 1/s. After each trial, the patient repeated the sequence. On every third trial the same sequence recurred, without the patient's knowledge. About 20 per cent more of the recurrent sequences are correctly recalled compared to the non-recurrent sequences (Baddeley and Warrington, 1970; De Renzi, Faglioni and Previdi, 1977; Milner, 1971). Corsi's block test (Milner, 1971) is a visuospatial analogue of the auditory-verbal digit sequences task. The experimenter tapped a sequence at 1/s, on a set of 9 black randomly-placed blocks fixed in position on a black wooden board (200 mm × 220 mm). The patient had to reproduce the sequence. After establishing the patient's block span, 24 trials of sequences, one above this span, were given, with the same sequence recurring every third trial. Similar savings (±20 per cent) were expected on the repeated sequences (De Renzi *et al.*, 1977; Milner, 1971).

Tests of Disconnection

Matching random shapes between hands. The wire shapes were made by bending 2 mm wire into the four shapes described in Milner and Taylor (1972). There were 24 trials of same-different matching. Both hands of the patient were placed under a cloth screen and one of the shapes was placed in each hand. The patient was instructed to say whether these shapes were the same or different. In the second task one shape was placed in the patient's left or right hand and he/she was asked to remember it. When satisfied, he/she gave back the shape and was then given the four shapes one at a time in a pseudo-random order in either the same or opposite hand. The task required identification of the matching shape. There were 12 trials per hand combination. The test was also administered with a 15-s delay between the first and second stimulus shapes giving a measure of delayed nonverbal tactile memory.

A *dichotic monitoring task* (Geffen, Traub and Stierman, 1978) was used to assess language laterality and to test for suppression of left ear words in the callosum-sectioned patients. The dichotic tape had 4 different lists of 103 different monosyllabic high-frequency word pairs recorded on Channels 1 and 2 of a Sony TC-854 four channel tape recorder at one pair per 750 ms in a woman's voice. The mean absolute onset asynchrony between word pairs was 29 ms (SD = 19 ms) with neither channel consistently leading. The target word, dog, occurred 10 times on each channel per list. Each list also contained 10 distractor words sharing two phonemes with the target word (for example, log, dig, doll). The remaining words were phonemically dissimilar from the target word. The words were randomized except that target and distractor words did not occur simultaneously or successively within or between channels or on the first or last four pairs of the list. Two monaural lists of 164 words were similarly recorded, with each list containing 25 target, 25 distractor and 114 other words.

The patient's task was to press a response key with a forefinger when the target word was detected on either ear. Monaural performance was measured first with each list presented twice, once with a left-handed and once with the right-handed response. Two short practice dichotic tests were given, first with one and next with the other hand responding. Subjects were instructed to fixate a central cross on the wall at eye level. The 4 dichotic lists lasting 1.8 min each were then presented. The headphones were reversed after 2 lists were presented, and hand responding changed between lists in an LRLR or RLRL order. The entire session lasted 25 min.

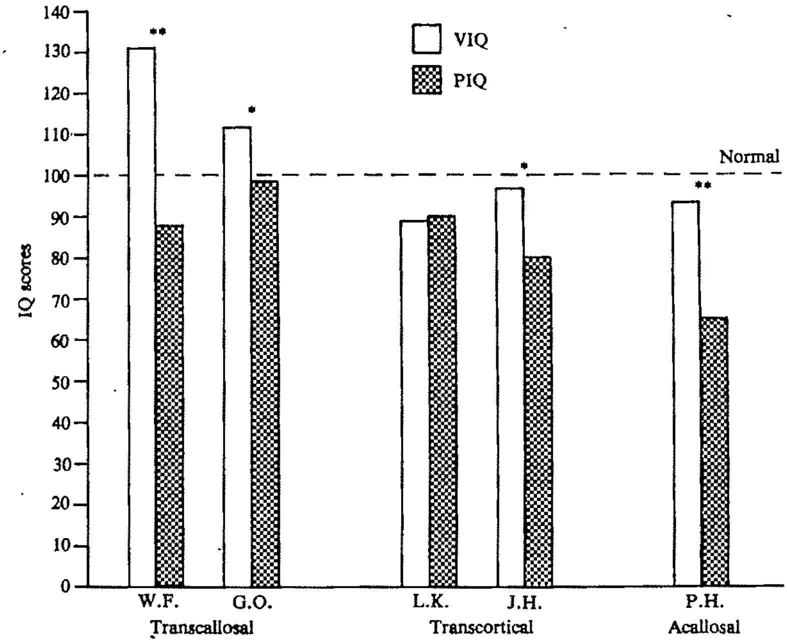

FIG. 2. Verbal (VIQ) and Performance (PIQ) scores on the WAIS. ** Difference significant at $P < 0.001$; * difference significant at $P < 0.01$; (Field, 1960).

RESULTS

Intelligence and Memory

Fig. 2 shows the Verbal (VIQ) and Performance (PIQ) scores for the 5 patients on the WAIS. For all patients except L.K. the PIQ was significantly lower than the VIQ, $P < 0.01$ (Field, 1960). While these results may reflect pre-operative ventricular dilation it appears that the patients who had the right hemisphere lesioned (J.H.) or retracted (W.F., G.O.) showed an expected PIQ deficit. L.K.'s operative approach was through her left middle temporal gyrus; however, her VIQ and PIQ scores were very similar.

WMS memory quotients (MQ) along with WAIS Full Scale IQs are presented in fig. 3, with the corresponding scores from Zaidel and Sperry (1974) for their total and partial commissure-sectioned patients. All patients except G.O. scored higher on the WAIS than the WMS. It should be noted, however, that only W.F. (transcallosal) showed an IQ-MQ difference that is similar to Zaidel and Sperry's patients; the transcortical subjects have small (< 10 point) differences as has P.H. (acallosal); and G.O.'s memory quotient did not differ from his IQ.

Table 2 shows the scores on the WMS sub-tests expressed as a percentage of normal scores. In this study, Information, Orientation and Mental Control were performed adequately after both transcortical and partial commissure sections. On all other sub-tests the 2 transcortical subjects performed below the normal range

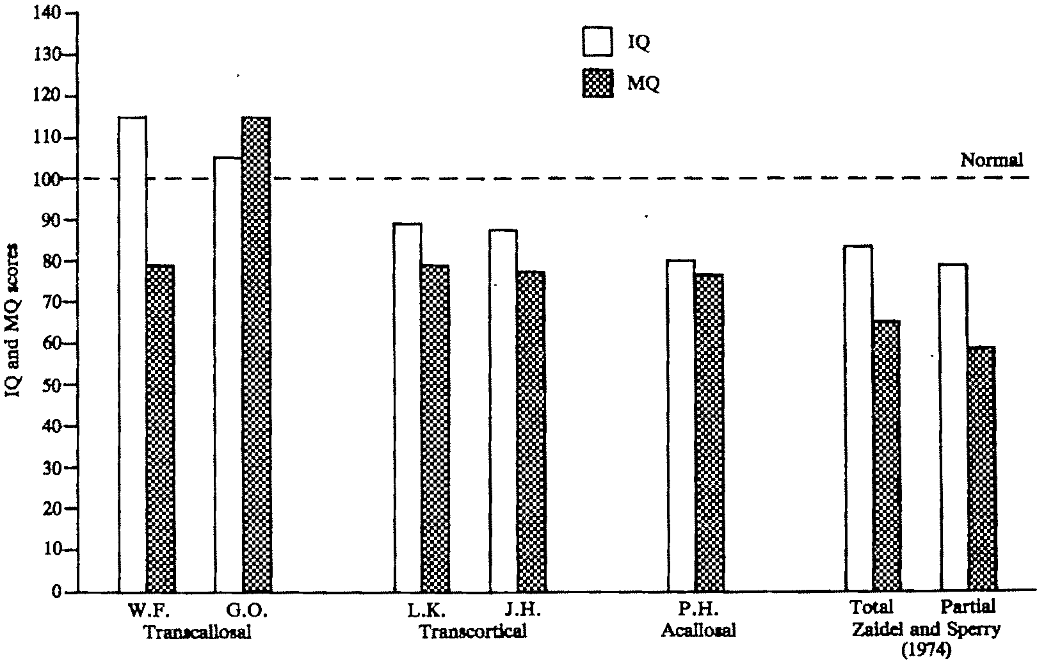

FIG. 3. Full scale IQ and Memory Quotient (MQ) on the WAIS and WMS for patients and for the total and partial commissure-sectioned patients of Zaidel and Sperry (1974).

TABLE 2. COMPARISON OF PERFORMANCE ON WMS SUB-TESTS OF TRANSCORTICAL, ACALLOSAL AND TRANSCALLOSAL ADULT PATIENTS IN THIS REPORT AND THE MEAN SCORES OF THE PARTIAL AND COMPLETE COMMISSURE SECTIONS OF ZAIDEL AND SPERRY (1974).

				Partial Commissure section			
	Transcortical		*Acallosal*				*Total commissure section*
Sub-test	*L.K.*	*J.H.*	*P.H.*	*G.O.*	*W.F.*	*(Zaidel and Sperry)*	*(Zaidel and Sperry)*
Information	100	100	80	88	100	42	65
Orientation	100	100	100	100	100	76	52
Mental Control	116	116	93	91	80	50	62
Story Passages	70	50	75	124	54	32	63
Digit Span	59	90	98	97	114	76	67
Visual Reproduction	75	59	64	108	82	41	34
Associative Learning { Easy	75	70	64	103	70	73	70
Associative Learning { Hard	14	14	14	88	0	14	16

Scores are expressed as a percentage of the normal score for the relevant ages (Wechsler, 1945).

with the exception of J.H. on Digit Span. The transcallosals, however, performed within normal limits with the exception of W.F. on Story Passages and Associative Learning. It would seem then that G.O., who underwent a transcallosal approach with minor damage to the right fornix, was alone in escaping memory deficits as measured by this test. All the patients performed better than Zaidel and Sperry's on Information, Orientation and Mental Control. On the other 4 sub-tests only G.O., who had neither fornix nor cortical damage to any significant extent, was remarkably free of deficits. On the memory functions tested, these results seem to implicate the fornices and the cortex to a greater extent than the body of the corpus callosum.

TABLE 3. DESIGNS CORRECT (8/10 = NORMAL) AND ERRORS MADE ON THE BENTON VISUAL RETENTION TEST

	Correct		*Errors*	
Patient	*0 s*	*15 s*	*0 s*	*15 s*
Transcallosal				
W.F.	6	5	6	10
G.O.	5	3	12	12
Transcortical				
L.K.	6	5	6	7
J.H.	5	3	8	15
Acallosal				
P.H.	5	5	14	11

The results of the BVRT are presented in Table 3. With no delay, all 5 patients performed well below average and obtained scores that were lower than the expected scores predicted on the basis of their own IQs. This finding is consistent with the performance of brain-damaged populations, particularly right hemisphere damage (Benton, 1955). However, all subjects in the present investigation outperformed 9/10 of Zaidel and Sperry's (1974) subjects. The correct scores did not distinguish between the two groups of patients; however G.O. and P.H. made many more errors than the other patients. In the delayed recall condition, only J.H. (transcortical) showed a higher than expected increase in errors. In terms of designs correct, none of the patients showed an abnormal decrement in the delayed compared to the immediate condition. Benton (1955) notes that the normal decrement with a 15 s delay is to get 2/10 less designs correct and to increase the error score by more than two points.

A significant (±20 per cent) saving on recurrent sequences was expected in the cumulative learning tasks. The only patients to reach this were G.O. (digits), J.H. (blocks) and P.H. (blocks). The transcallosal patients showed some savings for digits but zero or negative scores for blocks. The acallosal (P.H.) reversed this order.

The other transcortical patient (L.K.) showed zero or negative savings on both digits and blocks. The lack of learning shown in the repeated sequences was due to perseverative serial errors on the recurrent sequences (P.H.—digits; G.O., P.H., L.K.—blocks) indicating that it was recognized, but order errors were not corrected.

In conclusion then, with respect to the tests of Intelligence and Memory, *all* patients have suffered some loss of ability. The callosum-sectioned patient without significant fornix damage (G.O.) appears to have retained relatively more intellectual and memory functioning than either the patients with transcortical section, or the other callosum-sectioned adult with bilateral fornix transection.

In the *tactile matching task*, with simultaneous matching, W.F. (transcallosal) showed an inability to transfer tactile information. J.H. (transcortical) also made many errors which is consistent with damage to the right hemisphere (Milner, 1971). With successive matching at no delay, W.F. confirmed her transfer deficit with many more errors in the crossed (LR, RL) than the uncrossed (LL, RR) conditions. The 15-s delay increased the LL but not the RR errors for W.F., indicating that her left hemisphere probably subserves spatial memory functions. G.O., with a section of the callosum in the same area as W.F., showed no tactile transfer or tactile memory deficits at all. L.K. likewise showed no deficits. The acallosal, P.H., could successfully match simultaneous shapes; however, with successive shapes, he showed poor performance whenever his left hand was involved, and the delayed condition revealed a spatial memory deficit. It is likely that he lacks right hemispheric specialization for this task.

In the *monaural listening task*, all the patients achieved high target detection rates with no significant differences between the ears.

The hit rates for the patients, and for a normal group (Geffen and Traub, 1979) on the *dichotic test* are presented in fig. 4. All the patients except P.H. obtained a significant ($P < 0.05$) right ear advantage indicating left hemispheric dominance for speech perception. G.O. showed auditory disconnection with no targets detected on the left ear. J.H. showed evidence of her right cortical damage having a low hit rate on her left ear. L.K. did not show any abnormal result, indicating that her left temporal lesion has not affected structures relating to speech perception. This is consistent with the absence of language comprehension difficulties post-operatively as well as the similarity between her VIQ and PIQ scores. P.H. showed equal hit rates to targets in either ear which was expected, and this concurs with his performance when previously tested (Jeeves *et al.*, 1979).

DISCUSSION

The results indicate that the least memory deficit was found in G.O., one of the callosum-sectioned patients. His MQ was normal and very similar to his IQ. His performance on the other memory tests (BVRT, cumulative learning) similarly showed few deficits relative to the other patients in this study and to Zaidel and Sperry's patients. He showed no tactile disconnection and no tactile memory deficit.

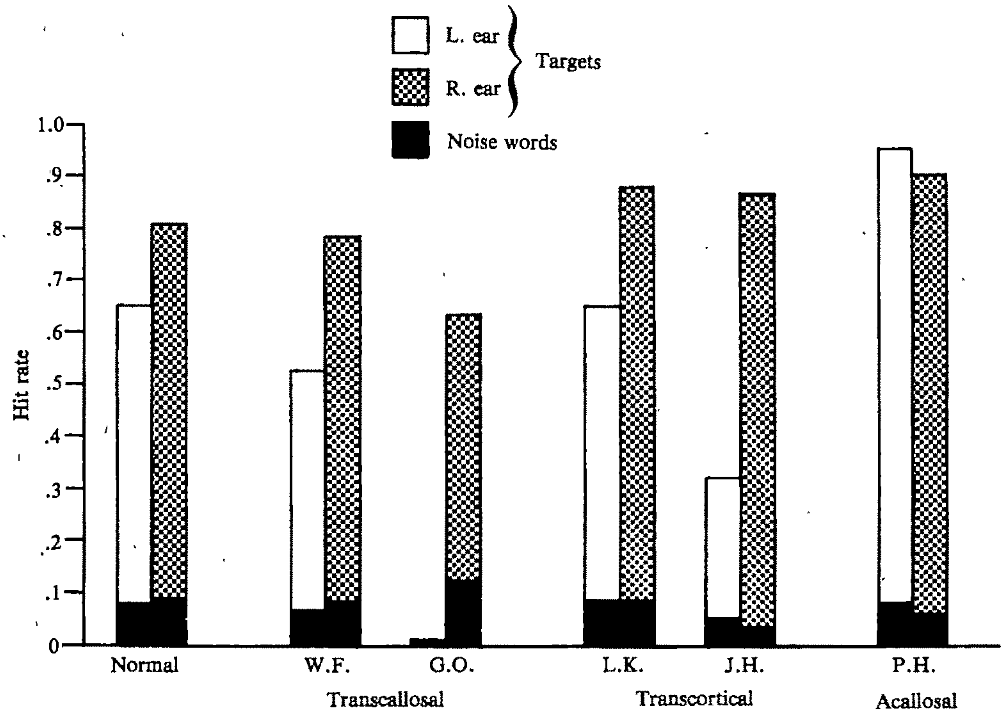

FIG. 4. Dichotic hit and false positive (responses to noise words) rates for adult patients compared to 31 right-handed normal adults (Geffen and Traub, 1979).

He did, however, show auditory disconnection, that is, total suppression of the left ear input in the dichotic task even though his monaural scores were equal between ears. Suppression of information in the left ear with different words to each ear is a common finding in cases of partial and total section of the corpus callosum (*see* Geffen, 1980). Different, simultaneous, verbal stimulation to each ear would be a rare occurrence in everyday life, thus G.O., despite his age (69 years) has minimal permanent deficits as measured by these tests. However, W.F., who also had a colloid cyst of the third ventricle of comparable size removed by the same approach was found to have a much lower MQ than IQ. The differences in operative procedure were that a larger draining vein in the frontal region was sacrificed, and whereas G.O. had minor right fornix damage, W.F. sustained bilateral anterior fornix damage. Zaidel and Sperry (1974) report that 'the surgical approach to the anterior commissure involved the columns of the fornix' (p. 264), and their patients showed the same low MQ and poor memory performance as W.F.

Horel (1978) in a comprehensive review of the neuroanatomy of amnesia argues that the deficits in memory found in patients with medial temporal lobe damage arise not from damage to the hippocampus-fornix-mamillary bodies system but from damage to the temporal stem. Thus he writes: 'It is the argument of this paper that it is injury to the connections of the temporal cortex within the stem that is responsible for the amnesia which is seen in humans with medial temporal lobe lesions.' His review is relevant here since it includes *inter alia* a consideration of the evidence from the effects of colloid cysts of the third ventricle. He argues starting from the studies of Cairns and Mosberg (1951) and of Williams and Pennybacker (1954) that these cysts 'put pressure upon the walls of the third ventricle in the region of magnocellular medialis dorsalis and removal of the cyst, which interestingly usually involves transection of the fornix, generally produces a remission of symptoms'. He does not believe that associated symptoms are due to raised intraventricular pressure *per se*. At the same time he points out that the severe amnesia which has been attributed to damage to the hippocampus and mamillary bodies leads directly to the prediction that destroying the fornix which connects these two structures (Simpson, 1952) should also produce amnesia. He queries this implication on the grounds that studies have been reported in which fornix damage is involved but no memory impairment is evident or at least not detected. However, it is doubtful whether too much weight should be put upon some of the studies to which he refers (for example, Van Wagenen and Herren, 1940) since they cannot be regarded as those in which sensitive, well quantified techniques designed to detect memory deficits were used. The whole history of, for example, the study of the functions of the corpus callosum, based on the studies of Van Wagenen and Herren in the 1940s, with their largely negative findings, should make us cautious of leaning too heavily on studies with negative findings unless the techniques used may reasonably have been expected to reveal deficits if present. For this reason Horel's conclusion that normal memory functions can be present in the absence of an intact fornix should be treated with some reservations. At the same time, as he points out, the deficits reported as memory deficits have at times been confused with deficits of spatial orientation.

Heilman and Sypert (1977) also note that many authors report that ablation of the fornix did not induce an amnesic state. In their own study they found that lesions of the neural projections of the hippocampus to the mamillary bodies produce an anterograde amnesia for recent events with apparent sparing of immediate and remote memory. They suggest that disturbances of memory could occur when there is bilateral destruction of either the posterior columns or both the anterior columns and the hippocampal commissure (Heilman and Sypert 1977; Iversen 1976).

A comparison of W.F. with a patient described by Heilman and Sypert (1977) reveals remarkable similarities. Their patient's tumour was beneath the splenium, straddling the hippocampal commissure. It was removed by microsurgical techniques involving bilateral section of the posterior columns of the fornix with no significant damage to surrounding structures except perhaps the hippocampal commissure (not sectioned in W.F.). On the WAIS, their patient's VIQ-PIQ was 27 points (W.F., 44 points); VIQ-MQ was 47 points (W.F., 51 points); IQ-MQ was 36 points (W.F., 33 points), and their patient's digit span was 7 (forwards and backwards), the same as W.F.'s. The common problem appears to be the formation of new associations.

Memory disorders have been associated with third ventricle tumours, particularly when obstruction of the foramen of Monro causes increased intraventricular pressure (Williams and Pennybacker, 1954). However, of the 180 patients screened by Williams and Pennybacker, only 4 were selected for testing. All had gross memory deficits prior to operation and had mass lesions of the third ventricle. Two of the 4 patients died during operation for removal of the tumour. One patient, who had partial removal of the tumour, was said to have improved intellectual control but persistent memory deficits (reported only fifty-four days post-operatively). One patient's tumour was removed completely and he showed no memory deficits on formal testing sixteen days after his operation. Thus, the assumption that memory deficits persist after tumour removal is shown to be incorrect by the recovered patient of Williams and Pennybacker (1954), G.O. of this study, and J.H. (recovering) of this study who has normal cumulative learning for digits, and a non-significant IQ-MQ difference. The accumulated evidence appears to implicate bilateral lesions of the fornix in producing recent memory deficits. Tumours of the third and lateral ventricles may lead to *functional* fornical lesions either directly or due to increased intraventricular pressure.

It would seem that the view specifically implicating the corpus callosum in disturbances of recent memory (Zaidel and Sperry, 1974) may be questioned. The two transcallosal patients appear to have better preservation of intellectual functions than the two transcortical patients. Further support for this view comes from a recent study of Winston, Cavuzzuti and Atkins (1979), who report on 4 patients, all children, who had undergone anterior transcallosal surgery for third ventricular lesions and who showed none of the features classically described following disruption of the corpus callosum.

The acallosal (P.H.) patient's IQ-MQ difference was not large, but his dichotic monitoring results, BVRT performance, and tactile memory deficit all suggest that the corpus callosum is important developmentally in the establishment of hemispheric specialization (Dennis, 1976; Field, Ashton and White, 1978). However, the localization of transfer functions of the trunk of the corpus callosum have not been clarified by this study. W.F. showed a marked inability in the transfer of tactile information and G.O. showed only auditory disconnection. Individual differences in interhemispheric connections may account for these discrepancies. Precise localization of modality specific transfer functions requires histological confirmation of the extent of lesions.

SUMMARY

Intelligence and memory functions were tested in 2 patients in whom the corpus callosum had been partially sectioned to remove intraventricular cysts or tumours and in 2 patients in whom similarly-located cysts or tumours had been removed transcortically. A patient with congenital absence of the corpus callosum was also tested. Callosal lesions *per se* did not appear to be responsible for memory deficits.

ACKNOWLEDGEMENTS

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Requests for reprints should be sent to: G. Geffen, School of Social Sciences, The Flinders University of South Australia, Bedford Park, South Australia 5042, Australia.

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PARALYTIC RABIES
A CLINICO-PATHOLOGICAL STUDY

by J. S. CHOPRA, A. K. BANERJEE, J. M. K. MURTHY *and* S. R. PAL

(From the Departments of Neurology, Pathology and Virology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India)

INTRODUCTION

RABIES continues to be a serious health hazard in several parts of the world. Despite strict control in some countries, there is always a threat of infection due to increased and rapid communications. In its classical form, rabies is well recognized, but there is a paucity of information about rabies presenting as ascending paralysis, the patients dying without developing 'hydrophobic' symptoms (Banerjee and Chopra, 1974). This is believed to be uncommon. It is possible that many cases are misdiagnosed because the disease is not often recognized in this form, the more so when no history of an animal bite is forthcoming. These cases are sometimes clinically indistinguishable from Landry's paralysis. The situation is further complicated by the non-availability of diagnostic tests for either of these two conditions. The need for a thorough post-mortem examination in all fatal cases of ascending paralysis has therefore been re-emphasized (Banerjee and Chopra, 1974).

In many cases of this type there are clinical indications of peripheral nerve involvement, in addition to signs of damage to the central nervous system. There is, however, very little information on the pathology of peripheral nerves in rabies in general and in paralytic rabies in particular. In this paper the clinical and pathological features of 11 cases of paralytic rabies will be described, together with a microscopical study of the spinal cord, brain and peripheral nerves. Part of this material has already been reported briefly (Chopra and Banerjee, 1976; Banerjee, Chopra and Pal, 1977).

MATERIALS AND METHODS

The clinical features of 11 cases of paralytic rabies proved at autopsy were analysed. A detailed pathological study of spinal cord, brain and peripheral nerves was carried out. Paraffin sections were stained with hæmatoxylin and eosin and special stains were used wherever needed.

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[1] Requests for reprints to Professor J. S. Chopra, Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India.

Impression smears were made from Ammon's horn, cerebrum or cerebellum, depending upon which specimen was available. The moist slide was flooded with Seller's stain, allowed to remain for a few seconds, rinsed under the tap, and dried at room temperature without blotting. This preparation was then examined for Negri bodies (Tierkel, 1973). The mouse inoculation test was performed by the method described by Koprowski (1973).

Different nerves taken at autopsy were appropriately stained to study the myelin sheaths and axis cylinders, and to display peri- and endoneural fibrosis. Teasing was also performed. The method was that of Chopra, Hurwitz and Montgomery (1969).

OBSERVATIONS

There were 10 males and one female in this study and the mean age was 31.5 years (range 14–62 years). A history of dog bite was obtained in eight instances and one patient had been bitten on the lower limb by his pet cat. Two patients were not aware of any animal bite. Two of the dogs were still alive and healthy when the injured patients presented with paralytic symptoms. In these patients, the mean incubation period was forty-nine days (range 7–90 days). Only four patients had received a course of Semple's anti-rabies vaccination. Two of these had the shortest incubation periods, that is, seven and twelve days. The mean duration of illness before admission was six days (range 3–10 days). The mean interval between the onset of symptoms and death was 8.4 days (range 7–11 days).

The most frequent presenting symptoms were pain and paræsthesiæ at the site of the animal bite. These were followed by motor weakness in the affected limb (8 patients) and a rapid onset of motor paralysis in the other limbs. In 3 patients, there was simultaneous occurrence of weakness in all four limbs.

Motor weakness was present in all cases on admission. It was quadriplegic in 10 patients and triplegic in one. However, this patient developed quadriplegia while in hospital. Evidence of bulbar involvement was noted in 6 cases. Only in 3 patients was there mental excitement at the time of admission. In none of the cases was hydrophobia present. There was respiratory muscle involvement at the time of admission or during the course of illness in all cases and respiratory paralysis was the mode of death in 9. Persistent tachycardia was observed in 10 cases. In 2 patients who died of cardiac arrest, there was slow arrhythmia in one and ventricular tachycardia preterminally in the other.

Cerebrospinal fluid examination was carried out in 10 cases. There was pleocytosis in 4 cases and elevation of protein above 40 mg per cent in 6. Both abnormalities were observed in 2 cases.

Neuropathology

The most striking pathological feature was severe inflammation of the spinal cord (fig. 1). The inflammation was most marked in the anterior horns. The lumbar and lower dorsal segments were the most affected and the intensity of inflammation was less at higher levels. The inflammation was characterized by dense perivascular infiltration by lymphocytes and proliferation of microglial cells both in diffuse and nodular fashion (fig. 2). The nerve cell changes paralleled the degree of inflammation. The 3 cases with severe inflammation showed marked loss of nerve cells and advanced degeneration in the remaining cells. One case with mild inflammation showed preservation of a number of neurons, while 4 others showed alterations in shape and staining characters and loss of Nissl granules. Foci of fresh small hæmorrhage were seen in the anterior horns in 2 cases. The white matter of the cord showed extension of perivascular infiltration along the perivascular spaces. There was no myelin degeneration. The leptomeninges of the cord also showed mild lymphocytic infiltration in some cases. The dorsal root ganglia showed inflammation in all cases examined, along with proportionate disappearance and degeneration of the ganglion cells (fig. 3). The intensity of the inflammation, however, was mild to moderate and not as severe as within the cord in any case examined.

In the brain, inflammatory change, consisting of perivascular lymphocytic infiltration, was most consistently found in the medulla. In all the cases with clinical bulbar involvement there were inflammatory changes of variable degree in the medulla, but these were often focal. Severe changes in the medulla with frequent neuronophagia and microglial nodules were seen in 2 cases. In the rest of the brain perivascular lymphocytic infiltration was seen focally in 7 cases.

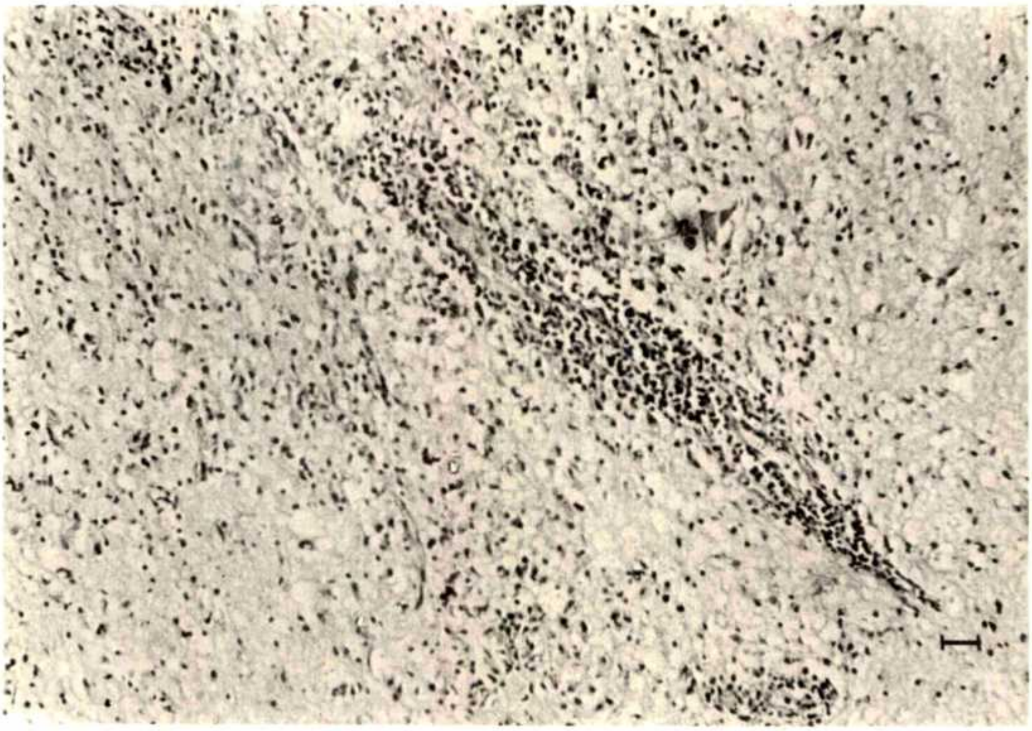

FIG. 1. Anterior horn of lumbar cord showing severe inflammation and marked loss of nerve cells. Few neurons present show degeneration (H and E. Bar = 30 μm).

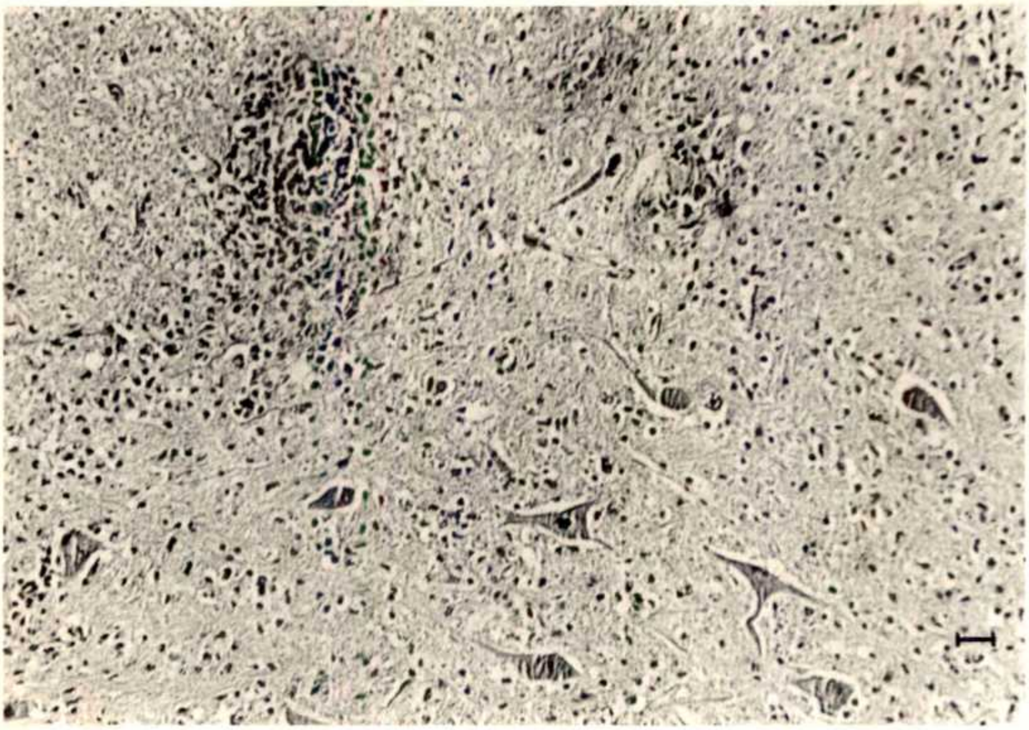

FIG. 2. Same area from another case showing relatively less severe inflammation and nerve cell changes (H and E. Bar = 30 μm).

Negri bodies were detected in paraffin sections stained with hæmatoxylin and eosin in all cases except 2, and in these they were seen only in the smears of fresh tissue. Special staining procedures were not found to be of particular help. The inclusions were most consistently detected in the Purkinje cells of the cerebellum (fig. 4) and the pyramidal neurons of the hippocampus. In the cerebral cortex inclusions were found in 3 cases and in dorsal root ganglia in one. Negri bodies could be demonstrated by animal inoculation in the 7 cases in which it was done.

Peripheral Nerves

In total 17 peripheral and 4 spinal nerves were studied. There was mild to moderate myelin fibre loss in 11 peripheral nerves (figs. 5, 6). Segmental demyelination and remyelination was present in 16 teased nerve preparations (figs. 7, 8 and 9 A, B, C). Axonal loss of variable degree was present in only 4 cases and Wallerian degeneration in teased single fibres was noted in 6 nerves (fig. 9D). In 9 nerves the primary abnormality was segmental demyelination and remyelination or myelin fibre loss either singly or in combination. In none of the cases was Wallerian degeneration seen as the only pathological feature. All the spinal nerves studied showed evidence of Wallerian degeneration as well as segmental demyelination. In

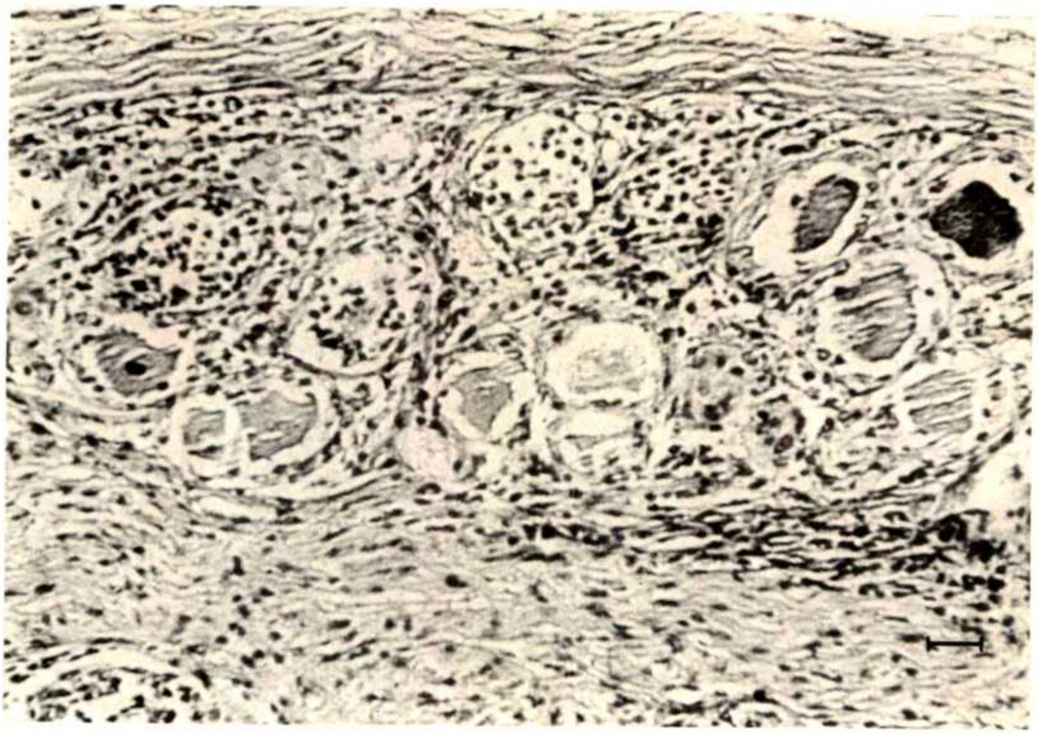

FIG. 3. Section of dorsal root ganglion showing moderate degree of inflammation (H and E. Bar = 30 μm).

one of these there was also infiltration by inflammatory cells (fig. 10). A peculiar paranodal bulb formation was seen in one of the spinal nerves (fig. 9 E). There was not much difference in the severity of the pathological changes between those patients who received anti-rabic vaccination and those who did not. In the one case bitten by a cat, there was a severe degree of segmental demyelination and remyelination and loss of myelinated fibres in paraffin sections (figs. 5, 6 and 7). The degree of pathological change had no relation to either incubation period or duration of illness.

DISCUSSION

Paralytic or 'dumb' rabies is far less familiar than the classical type. In the paralytic form, paralysis replaces the state of excitement of classical rabies. Less than a fifth of human rabies victims present with this type of disease (*Lancet*, 1978). The proportion may be higher in countries where rabies is still endemic. The reported average incubation period is between four weeks and eight to ten months (Love, 1944). In this study, it was forty-nine days. In two patients, it was less than one month. Both these patients received anti-rabies vaccination following the bite.

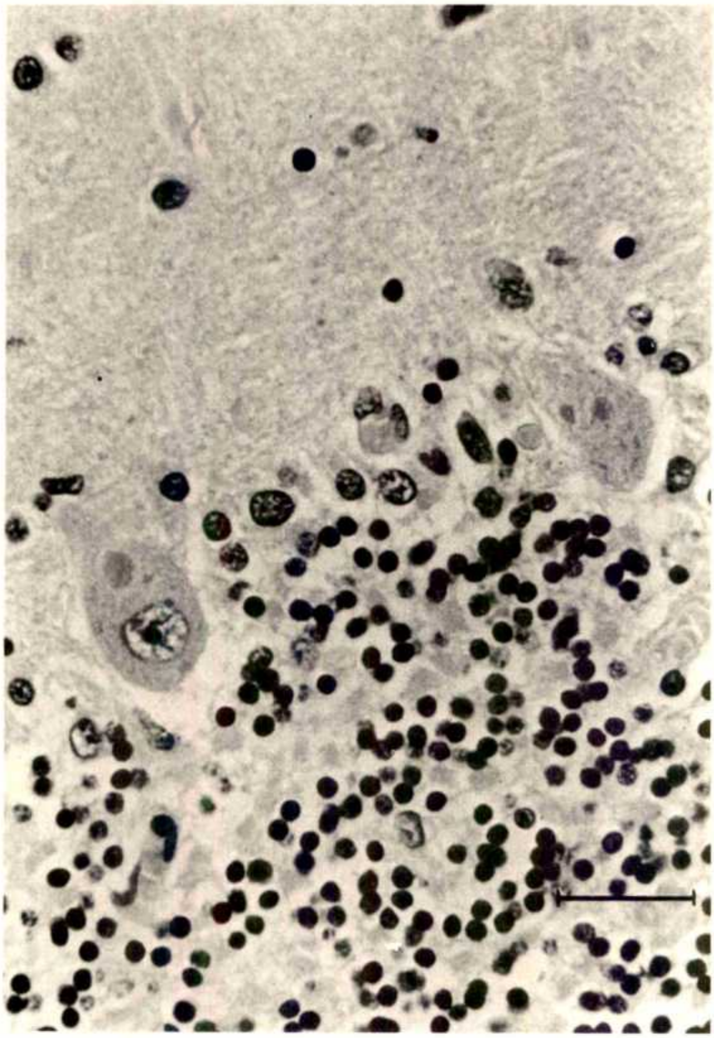

FIG. 4. Cerebellar Purkinje cells with Negri bodies. The cell without nucleus contains two inclusions (H and E. Bar = 30 μm).

The dog which had bitten our patient with an incubation period of seven days was alive and well at the time of the patient's death. It is well recognized that healthy dogs can secrete rabies virus in the saliva (Veeraraghavan, 1966–68, 1970; Fekadu, 1975). Veeraraghavan (1966–68, 1970) cited 7 cases of human rabies presumably resulting from bites by dogs which remained alive and well at the time of onset of the patient's illness. A history of animal bite was lacking in 2 cases. Such a history may not always be obtained in either classical or paralytic rabies (Vejjajiva and Tamthai, 1967; Knutti, 1929; Love, 1944). Paralysis may be localized to the limb bitten by the animal and may spread to other limbs, or may present from the onset as ascending paralysis of the Landry type, as seen in our patients. Although objective sensory deficit has been described (Hurst and Pawan, 1932; Pawan, 1939), in the present study it was observed in two instances only, although pain and paræsthesiæ were present in 9 cases.

Patients with paralytic rabies survive longer than those with classical rabies (Gamalia, 1887, quoted by Love, 1944). In this study, the mean duration of illness was 8.4 days whereas the reported mean duration of classical rabies is less than one week (Vejjajiva and Tamthai, 1967).

Death resulted from respiratory paralysis in 9 instances and in 2 it was due to cardiac dysrhythmia. It is interesting to note that there was persistent tachycardia in 10 cases. Similar observations were not made in earlier studies. Thus, as in classical rabies (Bhatt, Hattwick, Gerdsen, Emmons and Johnson, 1974), disturbance of cardiac rhythm is one of the potential modes of death.

In classical rabies slight elevation of CSF pressure and mild rise in protein (up to 60 mg per cent) has been described. There can be pleocytosis, particularly in the meningeal form (Atanasiu and Gamet, 1978). The present study has shown similar CSF findings in some patients with paralytic rabies which suggests that CSF examination is not helpful in the diagnosis of this illness.

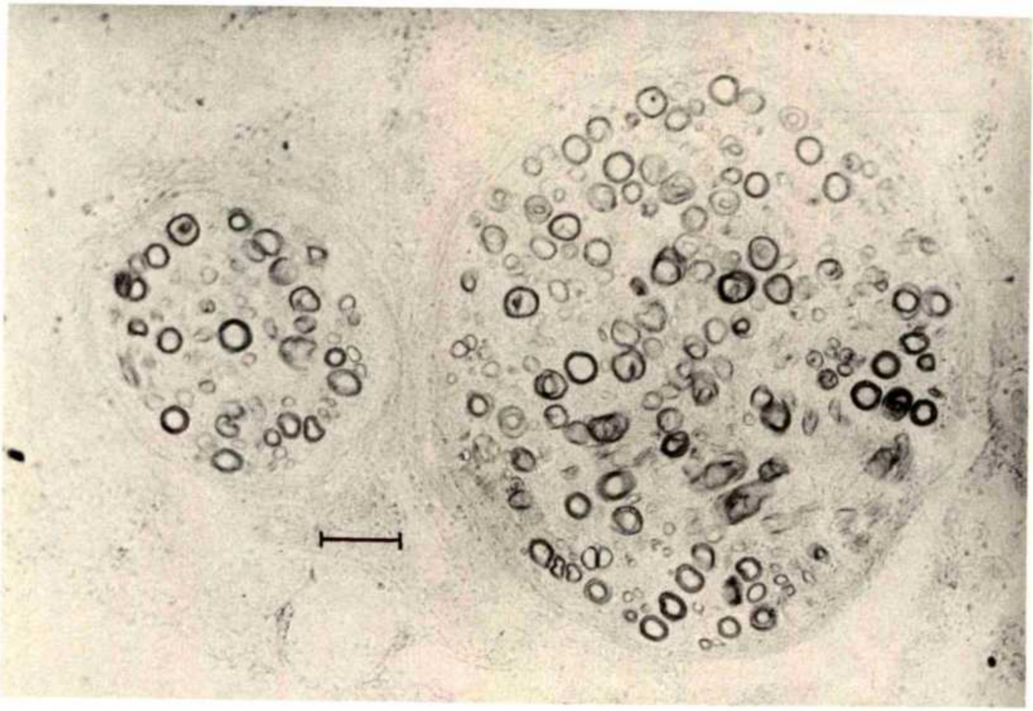

FIG. 5. Sural nerve fascicles (TS) showing moderate loss of myelinated nerve fibres in case of cat-bite (Kultschitsky. Bar = 30 μm).

It is obvious that paralytic rabies is not very rare, at least in developing countries where rabies is still an endemic disease. It may be difficult to differentiate from post-vaccinal encephalomyelitis, as in 4 of the present cases. The presence of local paræsthesiæ at the site of an animal bite, with paralysis, are the helpful clinical pointers which will suggest the diagnosis of paralytic rabies. The real difficulty arises when there is no history of animal bite and the patient presents with ascending paralysis of the Landry type. In such cases measurement of antibody titres in the serum could be of diagnostic help (Bhatt *et al*., 1974; Maton, Pollard and Davis, 1976).

Paralytic rabies is more likely to develop after a minor and insignificant bite (Love, 1944). The association of human paralytic rabies with vampire bite (Pawan, 1936), cat bite (Hurst and Pawan, 1932) and squirrel bite (Knutti, 1929) suggests that there may be alterations of the virus properties by passage in these animals. The present study supports the contention that the properties of the virus of paralytic rabies may be different from that of classical rabies. Host factors may also be important, as 2 patients were bitten by dogs which were perhaps carriers only as they did not develop rabies. Moreover 4 patients developed symptoms in spite of anti-rabies vaccination, and one of them had not only received anti-rabies vaccination, but the dog that had bitten him was alive and healthy, and the patient had the shortest incubation period (seven days) of any hitherto described.

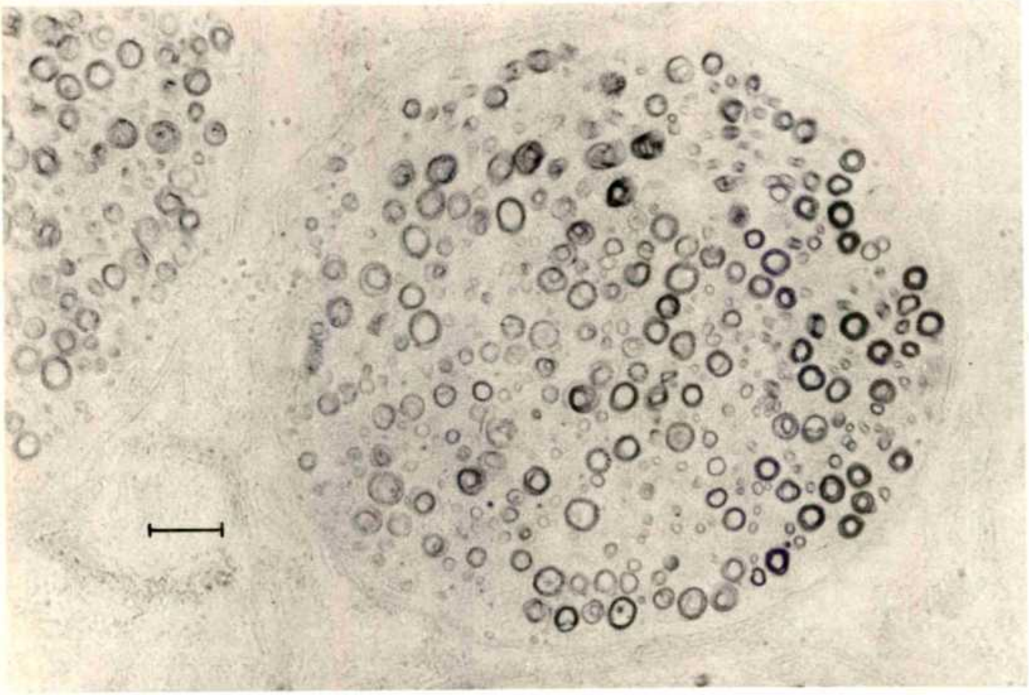

FIG. 6. Lateral popliteal nerve fascicles (TS) showing mild to moderate loss of myelinated nerve fibres. Same case as fig. 5 (Kultschitsky. Bar = 30 μm).

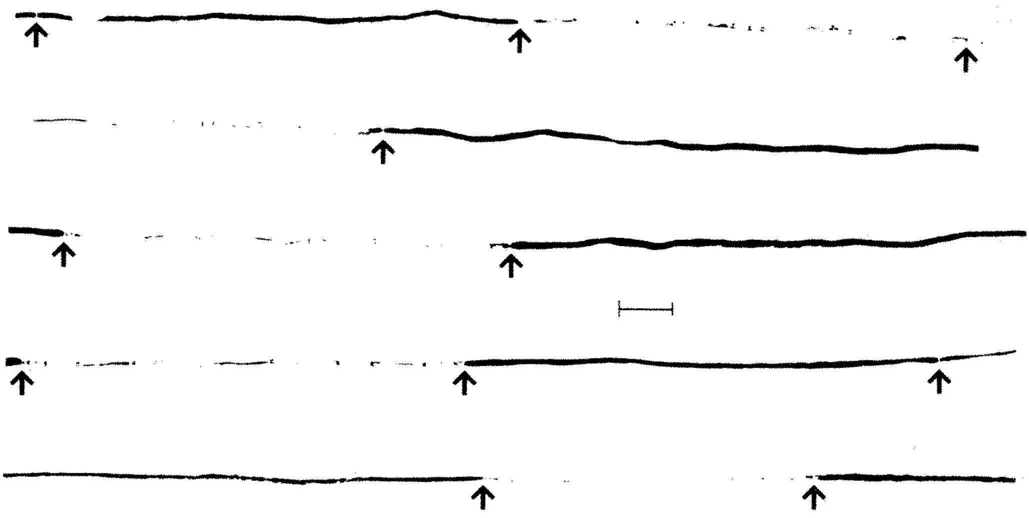

FIG. 7

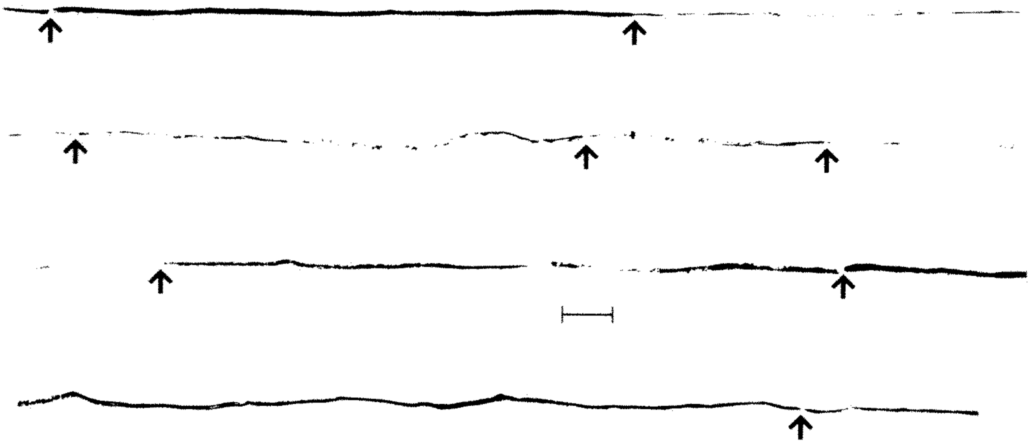

FIG. 8

FIGS. 7 and 8. Teased single nerve fibres from ulnar and lateral popliteal nerves showing segmental demyelination and remyelination. Same case as figs. 5 and 6 (Osmium Tetroxide. Bar = 50 μm).

Histological features observed in this study comprised (i) an inflammatory cellular reaction (ii) vascular changes and (iii) inclusion bodies. Similar features were noted in classical human rabies encephalomyelitis (Tangchai, Yenbutr and Vejjajiva, 1970). However, the distribution is different. In the paralytic form the brunt is born by the spinal cord followed by the brain-stem, with widespread nerve cell destruction and considerable microglial proliferation and perivascular infiltration. In classical rabies the inflammatory reaction, vascular changes and inclusion bodies are found much more in the thalamus, hypothalamus, cerebellum and cortex, in addition to those in the brain-stem and spinal cord. The number of cases of classical rabies encephalomyelitis in which Negri bodies were present in the cortex, hippocampus, thalamus and hypothalamus was greater (Tangchai *et al.*, 1970); in only 3 cases in our series were inclusion bodies present in the cortex. Lumbar and lower dorsal segments of the spinal cord were the parts most affected in this study.

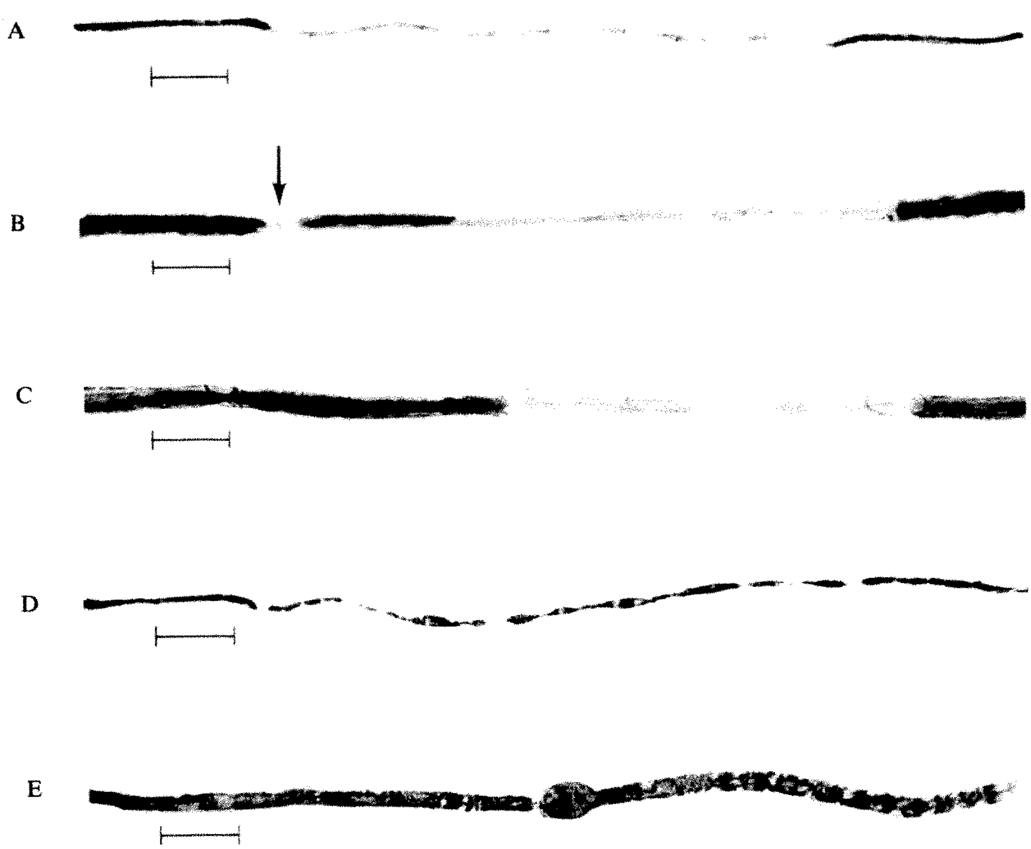

FIG. 9. Teased single nerve fibres showing A, a remyelinated segment; B, paranodal retraction (arrow) and demyelinated segment; C, segmental demyelination; D, Wallerian degeneration; E, paranodal bulb (Osmium tetroxide. Bar = A, D = 25 μm, B, C, E = 50 μm).

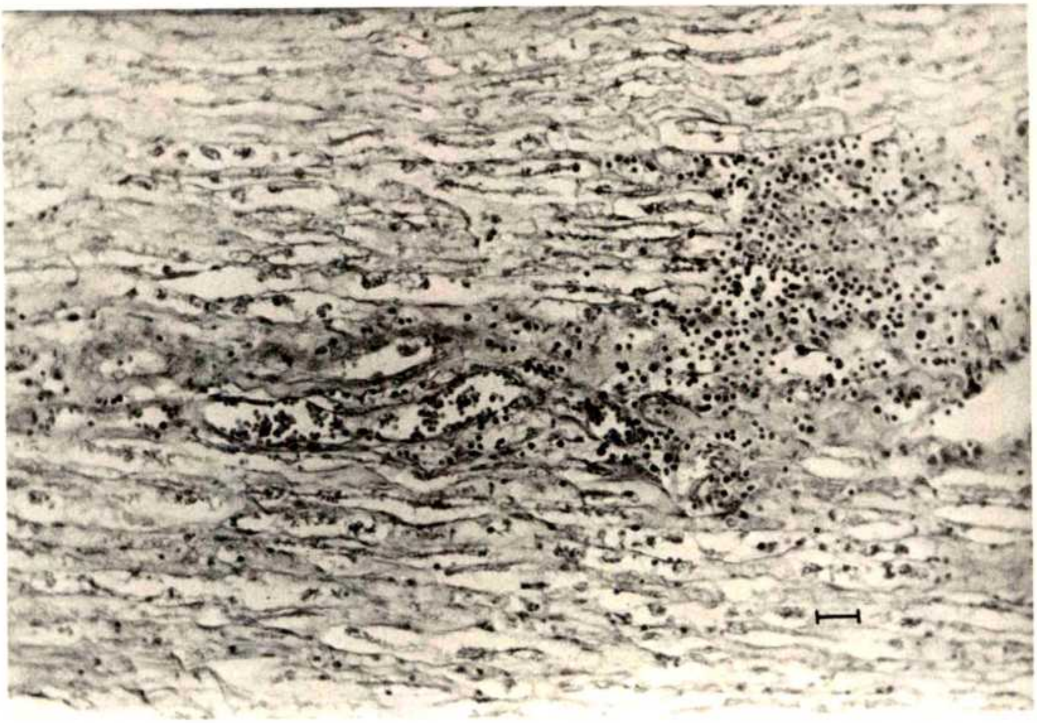

FIG. 10. Anterior spinal nerve root from Case No. 1 showing inflammatory cell infiltration (H and E. Bar = 30 μm).

The intensity of inflammation diminished at the higher levels. All 6 patients with bulbar involvement showed a variable degree of pathological involvement of the medulla, a good clinicopathological correlation. We found no correlation between severity of pathological lesions in the spinal cord and incubation period, as noted in classical rabies by Tangchai *et al.* (1970).

Hurst and Pawan (1932) showed lymphocytic infiltration in the sciatic nerves in one of their cases. Knutti (1929) showed lesions varying from slight focal necrosis to extensive necrosis, and destructive changes in the nerve roots arising from the dorsal portion of the cord, whereas these changes were minimal in the ventral roots. To the best of our knowledge there is no study of paralytic rabies in which the peripheral nerves have been studied in greater detail than in our series. The histopathology of peripheral nerves comprised loss of axons and myelinated fibres in sections, and segmental demyelination, remyelination and Wallerian degeneration in teased preparations. The changes were of variable degree. There were nerves which showed only segmental demyelination and remyelination. In none of the cases was Wallerian degeneration the sole pathology. The nerves which showed Wallerian degeneration showed segmental demyelination in addition. It is interesting that

Wallerian degeneration was seen in all the spinal nerve roots studied. By comparison, histopathological examination of peripheral nerves in classical rabies has shown axonal changes, leucocytic inflammatory reaction and proliferation and hypertrophy of the Schwann cells (Tangchai and Vejjajiva, 1971). However, these authors had not studied single teased nerve preparations. It is generally agreed that rabies virus is transmitted from the site of exposure to the central nervous system *via* peripheral nerves. Recently, Garcia-Tamayo, Avilo-Mayor and Anzola-Perez (1972) have demonstrated virus particles within myelinated axons of trigeminal nerve roots and in the Gasserian ganglia of 2 rabies patients. Atanasiu and Sisman (1967) have shown virus particles in the Schwann cells, perineural tissue and intrafascicular spaces. Thus, the histological features noted in peripheral nerves both in classical rabies, and in paralytic rabies as seen in this study, may be a reflection of damage by virus. However, histopathological changes in nerves remote from the site of animal bite cannot be explained by transneural transport of rabies virus. Axonal degeneration in the spinal nerve roots could be secondary to neuronal death in the anterior horns and posterior root ganglia which showed considerable damage in this study. Viræmia in rabies infection, which could have explained widespread damage to peripheral nerves, has not been established (Rhodes and Van Rooyen, 1962). It is suggested that some protein component of rabies virus may be cross-reacting with myelin protein to produce primary demyelination in peripheral nerves. This would also explain the acute onset and severity of progression of symptoms in paralytic rabies, and those histological features in the peripheral nerves which are akin to those of the Landry-Guillan-Barré syndrome. The pathological features observed in the spinal cord and brain are likely to be due to virus infection.

SUMMARY

Clinical and pathological features of 11 cases of paralytic rabies have been described, with a detailed study of the peripheral nerves. The mean incubation period was forty-nine days (range 7–90 days). The mean interval between the onset of symptoms and death was 8.4 days (range 7–11 days). A history of animal bite was available in 9 cases. Pain and paræsthesiæ at the site of the bite, followed by paralysis, were the main presenting symptoms. Motor weakness and involvement of the respiratory muscles was present in all cases. Histopathological features in the spinal cord and brain were (i) an inflammatory cellular reaction, (ii) vascular changes and (iii) inclusion bodies. Pathological changes were more severe in the spinal cord and brain-stem than in the cerebral cortex. Peripheral nerves showed segmental demyelination and remyelination, Wallerian degeneration, myelinated fibre loss and axonal loss. The changes were of variable degree. In 9 nerves segmental demyelination was the primary lesion. Wallerian degeneration and segmental demyelination were seen in 6 peripheral nerves. All the spinal nerves showed evidence of Wallerian degeneration as well as segmental demyelination. It is

suggested that some protein component of rabies virus may produce primary demyelination in peripheral nerves by a cross-antigenic action on myelin protein, but that the pathological features in the spinal cord and brain are due to virus infection *per se*.

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THE EFFECT OF SPINAL CORD STIMULATION ON FUNCTION IN PATIENTS WITH MULTIPLE SCLEROSIS

by D. J. READ, W. B. MATTHEWS *and* R. H. HIGSON

(From the University Department of Clinical Neurology and the Department of Urological Surgery, Churchill Hospital, Oxford, and the University Department of Radiology, Radcliffe Infirmary, Oxford)

INTRODUCTION

SPINAL cord stimulation *via* epidural electrodes has been used to treat intractable pain since 1967 (Shealey, Mortimer and Reswick, 1967; Shealey, Mortimer and Hagfors, 1970; Nashold and Friedman, 1972). A fortuitous observation of apparent neurological improvement during cord stimulation for pain in a patient with multiple sclerosis (MS) (Cook and Weinstein, 1973) encouraged the use of this technique for symptomatic relief in a variety of unrelated chronic neurological conditions (Proceedings of the 6th International Symposium on External Control of Human Extremities, 1978) of which MS has been the commonest. Of the published series claiming success for this treatment in MS (Cook and Weinstein, 1973; Cook, 1976; Dooley, 1977) only one (Illis, Sedgwick, Oygar and Sabbahi Awadalla, 1976) has shown evidence of careful study of the small number (two) of patients involved. Improvement in bladder function was not mentioned in the original paper though subsequent reports (Illis *et al.*, 1976; Cook, 1976; Dooley, 1977; Dooley, Sharkey, Keller and Kasprák, 1978; Tallis, Illis and Sedgwick, 1978; Campos, Dimitrijevic and Sharkey, 1978; Hawkes, Wyke, Desmond, Bultitude, Small, Jones and Robinson, 1978; Davis, Flitter, Bolton and Komrad, 1978; Waltz and Pani, 1978) have described varying degrees of benefit from cord stimulation on urinary dysfunction although few have attempted objective assessment. Because of the uncritical nature of much of the evidence in support of a beneficial effect of cord stimulation, we embarked on a detailed study of an initial group of 11 patients with chronic static or slowly progressive spinal MS, and an additional group of 5 patients, 4 with static MS and one with neurogenic bladder dysfunction of unknown cause.

METHODS

A. *Patients* (*Table I*)

Fully informed consent was obtained from all the patients, many of whom had heard of this treatment from other sources and had asked for an opportunity to try it. A policy of active discouragement was followed in potential cases where it was thought that the patient had misgivings.

Eleven patients were initially studied, 4 female and 7 males with an average age of 43 years (range 31 to 62 years). All had definite MS of the chronic static or slowly progressive spinal variety. The average duration of symptoms was twelve years with a range of five to twenty-six years, and none had had a relapse in the four years prior to stimulation. All were able to walk at least 100 m with or without walking aids and all lived independent lives. None was on any specific drugs except vitamin supplements and Naudicelle (a mixture of poly-unsaturated linoleic and linolenic acids—Bio Oils Research). In addition to a spastic paraparesis, one patient had ataxic nystagmus and ataxic upper limbs and 5 other patients had clumsiness or weakness of one or both arms, though in only one was this disabling. Bladder dysfunction accompanied the spastic paraparesis in all the patients and was the major problem in one. One patient had mild arterial hypertension and 2 had lower limb pain thought to be due to MS. One further patient had recently-diagnosed mild ulcerative colitis for which he was taking sulphasalazine. Assessment of these 11 patients having shown improvement in only two areas—bladder function and lower limb spasticity—a further 4 patients with definite MS and one with neurogenic bladder dysfunction of unknown cause were treated. Three were female and 2 male; the age and duration of disease ranges were similar to the original group. The 4 patients with MS led restricted lives because of weakness and spasticity of the legs.

TABLE 1. DETAILS OF INDIVIDUAL PATIENTS WITH POSITION OF EPIDURAL ELECTRODES

Patient			*Duration of multiple sclerosis*	*Neurological disabilities additional to spastic paraparesis and bladder dysfunction*	*Other features*	*Electrode placement vertebral level*
No.	*Age*	*Sex*	*(yrs)*			
1	45	M	9			D9–D10
2	31	M	10	Ataxic upper limbs	Ulcerative colitis. (Four months)	D5–D7 and D10–D12
3	45	M	15	Weak spastic R. upper limb		D2–D4
4	54	M	17	Weak L. upper limb		D3–D4
5	42	M	5	Ataxic upper limbs. Nystagmus		D3–D5
6	39	F	10	Ataxic upper limbs		D2–D3
7	50	M	18		'Central' pain lower limbs	D7–D8
8	35	F	10			D7–D9
9	62	F	26	Trigeminal neuralgia		D3–D5
10	34	M	5	Ataxic L. upper limb		D10–D12
11	32	F	7	Ataxic R. upper limb	Hypertension	D4–D5
12	56	M	16			D9–D10
13	36	F	*			D6–D8
14	34	F	6	Ataxia. Dysarthria. Diplopia. Wheelchair-bound		D6–D7
15	37	M	7	Ataxic L. arm. Wheelchair-bound		D9–D10
16	55	F	16	Weak R. arm	Ulcerative colitis. Total colectomy in 1957	D5–D7

* Does not have MS, but an idiopathic neurogenic bladder of ten years' duration with no other symptoms or signs.

The average duration of bladder dysfunction in the combined group of 16 patients was seven years with a range of three to fifteen years. All the male patients had varying degrees of impotence and most had bowel disturbance as well—constipation in the majority and occasional incontinence in three. Two patients had indwelling catheters, one a female for six months because of incontinence, and the other a male for four months because of retention with overflow requiring a condom appliance. Three other female patients gave a long history of dribbling incontinence (requiring permanent pad wearing) for three, six and eight years, respectively. One of these had no other evidence of organic nervous disease and had failed to respond to several prolonged bladder distensions; another had had three bladder distensions, a fascial sling operation and a sacral nerve crush, all without effect.

The remaining patients all had frequency and urgency and most had hesitancy, a poor stream and nocturia. They had all failed to respond to the appropriate drug treatment.

B. *Procedure*

With the patient lying prone on an x-ray screening table, two 16-gauge Hustead epidural needles were inserted under local anæsthetic and aseptic conditions as described by Illis *et al.* (1976). The platinum tipped Teflon covered stainless steel electrodes (Ceramic Substrates and Components, Farnham Common, Bucks.) were manœuvred into position in the posterior epidural space under x-ray control and finally adjusted with the stimulator connected so that the patients experienced paræsthesiæ in the appropriate segmental band and in one or both legs. The needles were then withdrawn and the free ends of the electrodes coiled over the skin, sprayed with antiseptic powder, taped down and covered with a sterile dressing. The electrodes were later connected to the stimulator apparatus *via* a loop antenna inductively coupled to a receiver (Avery Co. Inc., Farmingdale, New York, USA). To date we have only carried out temporary stimulation: the system is made permanent by subcutaneously implanting the receiver to which the electrodes are attached.

Stimulation was continous throughout the two weeks with the current level adjusted by the patient to maintain the paræsthesiæ in the lower limbs without either loss of this sensation or production of painful sensations. Pulse width and frequency were fixed at 200 μs and 33 Hz, respectively.

In 6 of the patients the electrode tips were placed in the upper thoracic region and in the remaining 10 at the mid- or lower-thoracic vertebral level, with the tips one or two vertebral bodies apart in all cases. One patient had two sets of electrodes inserted at an interval of one week, one set at the lower and the other at the mid-thoracic level. Twenty-four hours bed rest was enforced after insertion of the electrodes and assessment started after a further twenty-four hours. Physiotherapy was discontinued during the period of stimulation.

C. *Assessment*

Prior to electrode insertion the first 11 patients underwent one week's inpatient physiotherapy at the beginning and end of which they were assessed on a battery of tests based on those designed by Tourtellotte and Potvin (1974). These tests were also repeated at the end of the first and second weeks of cord stimulation, that is, on a total of four occasions. The tests were carried out by the same observer at the same time of day and in the same relation to meals. Hot baths were forbidden on the day of the test and an attempt was made to keep the ambient temperature as constant as possible. Apart from assessment of bladder function, the tests were in four main groups:

1. *Lower limb function.* (a) Walking time over 25 m. With walking aids if used. Repeated immediately. Average time of the two taken.

(b) Tone—assessed clinically.

0 = normal
1 = slight 'catch' or barely detectable increase in tone
2 = easily detectable increase in tone
3 = spasticity overcome with difficulty
4 = spasticity not overcome.

Average of three attempts taken.

(c) Quadriceps strength. Measured in the sitting position with a short-excursion spring balance attached to a bar at the back of the chair and with the foot on a roller skate to minimize friction. The connecting straps were adjusted so that angular movement of the lower leg occurred as near as possible about the vertical. An average of three attempts taken for each leg.

(d) Straight leg raising from the horizontal. Highest angle attained taken, measured with a goniometer strapped to the leg.

2. *Sensory testing.* (a) Vibration sense thresholds at both index fingers and both great toes. Measured with the Biothesiometer (Bio-Medical Instrument Co., Newbury, Ohio, USA). Average of three attempts taken.

(b) Joint position sense. Both index fingers and both great toes. Set pattern of ten random movements—mistakes scored.

(c) Two point discrimination threshold—at both index fingers.

3. *Manual dexterity.* All tests were carried out on dominant and non-dominant sides.

(a) Grip strength using standard hand dynamometer (S. Cox Ltd., London). Average of three attempts.

(b) Hand and arm steadiness—measured by determining the smallest diameter hole in which a $\frac{1}{8}$ in diameter metal rod could be held for five seconds with the arm outstretched, and supported at the forearm.

(c) Speed and co-ordination—two tests using the Clay-Adams laboratory counter with eight alternating red and white keys. In the first test one key was depressed with the index finger as many times as possible in a ten-second period. In the second the red keys were depressed in sequence again with the index finger as fast as possible for a ten-second period. Average of three attempts for each test taken.

Each group of tests was preceded by a five-second 'familiarization' attempt.

4. *Videotape recording.* (a) A 10 m walk filmed from one side and end on.

(b) An attempt at putting on a pair of trousers (or tights).

(c) An attempt at undoing and doing up shirt buttons.

The tapes were edited and shown in random order to a panel of assessors (four physiotherapists and one clinical research officer) none of whom had had dealings with the patients. They were told that cord stimulation improved function and that 2 of the 4 films were before and 2 during stimulation: they were asked to assign each film to one of three categories—before, during or 'don't know'. No specific criteria were suggested on which the films should be judged and consultation was not allowed. For technical reasons one patient was not videotaped.

In addition to the above, the tests of lower limb function were performed every day at approximately the same time, before and during cord stimulation. Skin temperature of the exposed feet was measured daily throughout under standard conditions in 7 of the patients using a Hewlett-Packard digital thermometer with the sensing thermocouple taped to the dorsum of the foot. Daily tests of lower limb function only were carried out on the 4 additional patients with MS.

5. *Bladder function.* During the first week renal function was assessed with blood urea, electrolyte and serum creatinine estimations, intravenous urography and urine culture. Fluid intake was maintained at normal levels and daily micturition frequency and volume output recorded. For all but the first four patients a mictiograph (DISA) was available and twice daily urinary flow studies were recorded where possible.

The mictiograph records the flow pattern, maximum flow rate, total voiding time and voided volume for individual acts of micturition. This is accomplished by arranging for the urine to be passed into a wide-mouthed funnel whence it is allowed to fall on to a rotating plastic disc, variations in the speed of which are used to perform the necessary electronic calculations traced out on a single channel pen recorder.

At the end of the week full fluid urodynamic assessment was carried out. This included:

(a) an initial free voiding study before insertion of urethral catheters. Urine flow rate and volume of urine voided were measured;
(b) residual urine measurement;
(c) urethral pressure profile measurement using a Porges catheter (withdrawal speed 1 cm/s, perfusion rate 140 ml/hr);
(d) cystometry: the bladder was filled at 100 ml/min with saline at room temperature using a 12 FG urethral catheter. Intra-abdominal pressure was assessed by a fluid-filled catheter in the rectum;
(e) voiding study with simultaneous measurement of intra-vesical and intra-abdominal pressures, urine flow rate and volume and synchronous cineurethrocystography;
(f) sphincter EMG using a coaxial needle electrode inserted percutaneously through the perineum into the external urethral sphincter (Vereecken and Verduyn, 1970; Vereecken, Derluyn and Verduyn, 1975; Blaivas, Labib, Bavers and Retik, 1977). Forty-eight hours after electrode insertion the daily output charts were restarted with twice daily urinary flow studies. The full urodynamic assessment was repeated at the end of two weeks' stimulation;
(g) urodynamic terminology: except where otherwise defined, this is in accordance with the recommendations of the International Continence Society (1976, 1977), relevant definitions of which will be briefly summarized:
    (i) free voiding study: measurement of the time/volume relationships of fluid freely expelled through the urethra;
    (ii) cystometry: measurement of the pressure/volume relationships of the bladder;
    (iii) flow pattern: continuous or interrupted. Cannot be defined, best illustrated (*see* figs. 4, 5, 6, 7);
    (iv) flow rate: volume of fluid expelled *via* the urethra per unit time. Measured in ml/s;
    (v) voiding time: total duration of micturition including interruptions. Measured in seconds;
    (vi) voided volume: total volume of fluid expelled during micturition. Measured in ml;
    (vii) residual urine: volume of fluid remaining in the bladder at the end of micturition. Measured in ml;
    (viii) uninhibited detrusor: presence of contractions greater than 15 cm H_2O when the patient is asked to inhibit;
    (ix) urethral closure pressure profile: denotes intraluminal pressure along the length of the urethra with the bladder at rest. Measured in cm H_2O;
    (x) maximum urethral closure pressure: maximum pressure of the measured profile minus the bladder pressure. Measured in cm H_2O.

D. *Neurophysiological Investigations*

1. *Evoked potentials.* During the week before electrode insertion, cervical and cortical somatosensory (SEP), visual (VEP) and auditory brain-stem (BSEP) evoked potentials were recorded. The latter two were used only as additional diagnostic evidence and did not form part of the assessment protocol. The SEPs were recorded on two or more occasions at intervals during the two weeks' cord stimulation, using the technique of Small, Matthews and Small (1978). The cervical and short latency cortical waves evoked from the median nerves at both right and left wrists were then randomized and assessed blind by one of us (W.B.M.). For technical reasons, two patients did not have SEP recordings.

2. *Electromyography.* With the cord stimulation electrodes *in situ* three patients (Nos. 1, 7, 10) had coaxial needle electromyograms recorded from (i) the right rectus abdominis below the level of the umbilicus, and (ii) simultaneously from the right quadriceps femoris and biceps femoris. The patients were asked to relax completely and were allowed to do so with the stimulator apparatus switched off.

This was done because it was noticed clinically that spasticity and clonus could be induced or increased by increasing the voltage of stimulation to levels beyond those at which pleasant comfortable paræsthesiæ were experienced and some of the patients had noticed a tight abdominal feeling, relieved immediately on switching the stimulator off. Recordings were made under two sets of conditions: (i) with the cord stimulation voltage at a 'normal' setting (two patients) and at a setting sub-threshold for paræsthesiæ (one patient) with the frequency varied in steps from 7 Hz to 120 Hz; and (ii) with the frequency fixed at the 'normal' 33 Hz and the voltage increased (by the patient) to levels beyond those which were comfortable. Stimulating pulses were of alternating polarity and 200 μs in duration.

3. *Applied current measurements.* At one point, usually during the second week of cord stimulation, measurement of the applied voltage was made and current through and resistance between the epidural electrodes calculated. To make the measurements, the epidural electrodes were reconnected to the receiver with two short interposed bare single-stranded copper wires of $\simeq$ 0.5 mm diameter, one of which contained a 100 Ω resistor in series. When the patient had adjusted the voltage to 'normal', the voltage pulses between the two wires either side of the resistor and across the resistor were measured on a Gould oscilloscope (Model OS 4000) and Ohm's law applied. It was assumed that the 100 Ω series resistor was small compared with the interelectrode resistance and that the drop in current would therefore be negligible for the purposes of the calculation. The voltage across the electrodes was also measured in some patients with the 100 Ω resistor removed.

COMPLICATIONS

There were no medical complications, neither local nor spinal infections were encountered and antibiotics were not routinely given. The skin surrounding the electrode exit site was often slightly reddened but this always settled within a day of electrode withdrawal and did not give rise to any trouble even in the patients in whom the electrodes were left *in situ* for longer than the standard two weeks. The dura was never broached during electrode insertion and cerebrospinal fluid leaks did not occur.

Clonus and spasticity of the legs could readily be induced or increased in most of the patients by increasing the stimulation voltage to levels above those which were comfortable. In the three patients in whom coaxial needle electromyograms were recorded from the quadriceps and hamstring muscles, this was shown to be due to simultaneous tetanic contraction of both agonist and antagonist muscles.

No problems were encountered with any of the stimulating apparatus except for the electrodes. Various types were tried initially and discarded because of excess slippage (Avery) and in some cases disintegration of the electrode *in situ* (Davis and Geck). With the present type of solid stainless steel wires, 'guidability' is retained and the light weight minimizes the tendency to slip once positioned. Electrode placement and fixation remain, however, the commonest cause of difficulty.

RESULTS

1. *Lower Limb Function*

(a) Walking time (fig. 1). Five patients had consistent times under 40 s over the 25 m course, unaltered by either physiotherapy or cord stimulation. The remaining 6 patients had randomly fluctuating walking times over 40 seconds. During cord stimulation 3 improved marginally and 3 became worse.

(b) Tone (Table 2). In the 11 original patients physiotherapy was not shown to affect tone. Cord stimulation had no effect in 2 patients and reduced tone without a concomitant reduction in strength in 6 patients. One patient had normal leg tone throughout and in 2 tone increased during cord stimulation. Three of the additional 5 patients had increased tone prior to cord stimulation and 2 of these were unable to walk more than two or three steps. During cord stimulation tone was decreased in all 3, and the 2 previously chair-bound patients could walk for distances of 50 m and 20 m. These changes persisted for the duration of their temporary stimulation (four and eight weeks, respectively).

(c) Quadriceps strength remained unaltered or was increased slightly. No patient became weaker and one almost doubled the power in his weaker leg.

(d) Straight leg raising did not alter significantly in 7 patients and improved in the other 4.

2. *Sensory Testing*

(a) Upper limbs—no significant change in any modality was observed.

(b) Lower limbs—in 2 patients no changes occurred; in 4 there was minimal improvement and minimal deterioration was observed in the remaining 5 patients.

3. *Manual Dexterity*

Irrespective of the site of electrode placement only minor fluctuations in hand function were seen.

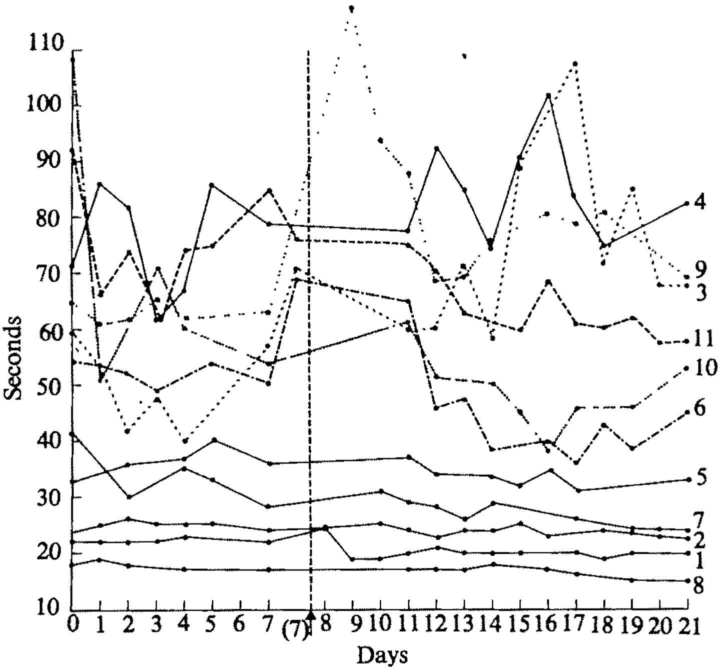

FIG. 1. Graphical representation of time taken to walk 25 m. Vertical dotted line indicates start of cord stimulation. Patient numbers at ends of lines.

4. *Videotaped Activities*

For ease of assessment only the sequences showing walking and putting on trousers or tights were used. In only 3 of the 10 were a majority of the walking tapes correctly assigned, indicating improvement; while in 6 there were varying degrees of mismatching, half of them almost complete, indicating a deleterious effect. On the other hand, 6 of the 10 had a majority of correctly assigned tapes for the dressing sequence.

5. *Urinary Bladder Function*

Renal function was normal in all patients and there was no evidence of dilation of the upper urinary tract on intravenous urography in any patient. Two patients were found to have infected urine at initial assessment which responded to antibiotic therapy. Insertion of electrodes was deferred in these patients until their urine was sterile.

TABLE 2. DAILY CLINICAL ASSESSMENT OF LEG TONE (*see* TEXT FOR SCALE)

		Before stimulation (days)						*During stimulation (days)*														
Patient	*Leg*	*1*	*2*	*3*	*4*	*5*	*6*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*Overall change*
1	R.	3	3	3	3	3	4			3	1	1	0	2	3	1	1	1	1		2	+
	L.	1	1	1	1	1	1			0	0	0	0	0	0	0	0	0	0		0	
2	R.	3	0	0	0	3	3			0	0	0	0		0	0	0	0	0		0	+
	L.	2	0	0	0	3	2			0	0	0	0		0	0	0	0	0		0	
3	R.	2	0	1	2	3	3			1	2	2			3	3	3	4	4	3	3	–
	L.	1	0	0	0	0	1			0	0	1			1	1	1	2	1	1	1	
4	R.	2	3	4	3	2	2			2	2	2	2		2	2	3	3	2	2	2	0
	L.	3	4	4	4	3	4			3	3	3	3		3	3	4	3	2	2	2	
5	R.	1	1	1	1	1	1			1	1	0	0		1	0	1	1	0		1	+
	L.	3	3	3	2	3	2			2	1	0	0		2	0	1	2	1		2	
6	R.	2	2	3	3	3	0			3	3	2			0	1	2	1	1	1	3	+
	L.	1	1	2	0	1	0			2	1	2			0	1	3	0	0	1	1	
7	R.	2	0	0	0	2	0			0	0	0	0		0	0	0	0	0		0	+
	L.	2	0	2	0	2	0			0	0	0	1		0	0	0	0	0		0	
9	R.	1	3	2	2	2	2			0	0	0	0		0	0	0	0	0		0	+
	L.	0	0	1	0	0	0			0	0	0	0		0	0	0	0	0		0	
10	R.	2	2	3	3	3	3			4	3	2			3	3	3	1	2		3	0
	L.	2	3	3	3	3	2			3	3	2			2	2	1	1	2		2	
11	R.	0	0	0	1	1	3			2	4	3		2	2	0	0	0	3		0	–
	L.	0	1	0	1	2	3			2	4	3		4	3	2	1	0	2		0	
12	R.	2	3	3	3				0				0	0	0	0	0					+
	L.	3	3	2	3				0				0	0	0	0	0					
14	R.	4	4	4	4	4			0	0			0	0	0	0	0	0		0	0	+
	L.	4	4	4	4	4			0	0			0	0	0	0	0	0		0	0	
15	R.	4	4	3	4	3	4		3	2			1	0	1	0	0	1		0	0	+
	L.	4	3	3	4	4	4		4	4			1	1	0	0	0	0		0	0	
16	R.	0	0	0	0				0	0	0		0	1	0	0	0					0
	L.	0	0	0	0				0	0	0		0	2	0	0	0					

Patients 8 and 13 had normal leg tone throughout and are not shown.

TABLE 3. IMPROVEMENT IN URINARY SYMPTOMS. PATIENTS' ASSESSMENT OF CHANGES IN SYMPTOMS SHOWN AND AVERAGED DAILY FREQUENCY RECORDS FOR COMPARISON

					Measured daily frequency (average)	
Patient	*Urgency*	*Hesitancy*	*Slow stream*	*Frequency*	*Before Stimulation*	*During Stimulation*
1	+	+	+	+	5.5	6.0
2	0	0	0	0	9.7	10.2
3	+	0	+	+	11.6	10.0
4	+	0	+	0	NA	NA
5	+	+	+	+	8.4	7.0
6	Catheter removed. Frequency and urgency present				NA	8.0
7	+	+	+	0	4.5	5.5
8	Continent by day. Much less leakage by night				NA	8.0
9	+	+	0	+	9.4	7.2
10	0	0	0	0	6.6	6.5
11	0	0	+	0	7.3	8.7
12	+	0	0	0	12.4	11
13	Became continent				NA	6.5
14	Became continent				NA	8.6
15	Catheter removed. Continence regained				NA	9.4
16	+	NA	NA	++	14	5

+ = improved. 0 = no change. NA = not available.

A. *Symptomatic Results*

These are shown in Table 3. Of the 16 patients, 4 denied any improvement (Nos. 2, 4, 6, 10). One of these (No. 6) had been catheterized for six months. The catheter was removed at the beginning of cord stimulation and her previous incontinence was then found to have resolved leaving her with frequency and urgency not altered by cord stimulation. The other 12 patients all reported overall improvement in symptoms.

In 6 patients this was pronounced. All 3 of the incontinent patients improved (Nos. 8, 13, 14): 2 were completely continent (Nos. 13, 14) and the third (No. 8) had continuing but much reduced nocturnal dribbling though even she was dry by day during cord stimulation. The male patient with an indwelling catheter (No. 15) had failed to micturate on the five occasions when attempts had been made to remove the catheter before cord stimulation. On the third day of stimulation the catheter was removed but absent urethral and bladder sensation resulted in dribbling incontinence. Four days later the return of urethral sensation allowed him to control

TABLE 4. URODYNAMIC MEASUREMENTS BEFORE AND DURING SPINAL CORD STIMULATION

Patient	*Max. free flow (ml/s)*		*Residual volume (ml)*		*Bladder capacity (cystometric) (ml)*		*Max. detrusor pressure during filling (cm H_2O)*		*Max. urethral closure pressure (cm H_2O)*		*Detrusor pressure at max. flow (cm H_2O)*		*Max. flow rate (ml/s)*	
	Before	*During*	*Before*	*During*	*Before*	*During*	*Before*	*During*	*Before*	*During*	*Before*	*During*	*Before*	*During*
1	NA	12	NA	300	100	480	> 75	> 75	65	60	70	50	8	12
2	NA	NA	NA	NA	50	50	> 75	> 75	60	90	50	NA	5	NA
3	6	NA	60	NA	460	410	> 75	> 75	80	60	40	50	8	8
4	7	10	0	0	580	650	30	30	130	95	80	NA	10	NA
5	NA	7	NA	25	50	50	> 75	> 75	110	80	NA	NA	NA	NA
6	NA*	12	NA	250	630	980	70	60	60	50	50	25	10	10
7	NA	NA	NA	NA	760	1000	> 75	70	60	50	60	NA	7	8
8	8	13	180	160	160	350	> 75	> 75	100	80	80	40	Dribble	30
9	NA	5	NA	225	425	490	55	> 75	45	40	80	80	1	2
10	NA	NA	NA	NA	760	700	> 75	> 75	80	60	60	30	10	10
11	NA	NA	NA	NA	420	75	> 75	> 75	130	90	80	100	0	0
12	NA	NA	NA	NA	50	80	> 75	> 75	65	50	NA	NA	NA	NA
13	NA	NA	NA	NA	50	220	> 75	> 75	70	50	NA	NA	NA	NA
14	9	5	320	780	800	1000	40	40	80	62	40	44	5	4
15	NA	NA	NA	NA	50	110	> 75	> 75	70	50	NA	NA	NA	NA
16	NA	5	NA	180	240	420	30	30	60	60	35	NA	5	Dribble

Details of urodynamic tests on single occasions before and after two weeks' cord stimulation. * Catheter *in situ.* NA = patient unable to perform the appropriate test (*see* text).

micturition partially and after a further week of cord stimulation he had discarded all appliances and was continent by day and night. One patient (No. 16) had a marked reduction in frequency and a further patient (No. 1) completely reversed his considerable voiding difficulty.

B. *Objective Results* (*Table 4*)

(i) Urine flow rate and residual volume: free flow rates were improved in 2 patients (Nos. 4, 8), decreased in one patient (No. 14) and 5 patients previously unable to void on command were able to do so during cord stimulation. In the remainder the voiding pattern was unchanged. The residual volume of urine decreased slightly in one patient (No. 8), increased in another (No. 14) and remained negligible in the third patient (No. 5) who had been able to void on command both before and during cord stimulation. One patient (No. 4) voided to completion with no residual urine both before and during cord stimulation.

(ii) Cystometry: cystometric capacity (which we defined as the bladder volume at which uncontrollable voiding occurred, or at which the patient felt uncomfortable) was increased in 11 patients, was unchanged in 2 and decreased in 3. The increase in capacity varied from 12 per cent to 380 per cent. All 16 patients had detrusor instability with detrusor pressures exceeding 15 cm of water during filling. Instability persisted in all except one patient during cord stimulation. In this patient (No. 16) instability was present in the first but absent in two subsequent cystometrograms performed on the same occasion.

(iii) Urethral closure pressure profile: the maximum urethral closure pressure was reduced in 14 of the 16 patients, increased in one (No. 2) and unchanged in one (No. 16).

(iv) Voiding studies: cineurethrocystography with synchronous measurement of maximum urine flow rate and detrusor pressure at maximum flow were satisfactorily performed in 8 patients (Nos. 1, 3, 6, 8, 9, 10, 11, 14) both before and during cord stimulation. Radiographic studies were possible only before stimulation in a further 2 patients (4, 16) as they were unable to initiate detrusor activity.

(a) Detrusor pressure at maximum flow rate: this was decreased in 4 (Nos. 1, 6, 8, 10), unchanged in one (9) and increased in 3 patients (Nos. 3, 11, 14). Two of the 4 in whom it was lower had a corresponding increase in maximum flow rate (Nos. 1, 8); and all 4 had a lower maximum urethral closure pressure.

(b) Synchronous cineurethrocystography: this demonstrated satisfactory opening of the bladder neck in 8 patients (Nos. 2, 3, 4, 6, 7, 10, 14, 16) and evidence of bladder neck narrowing in the other 2 (one male (No. 1) and one female (No. 9)) only one of whom, however, had urodynamic evidence of bladder outflow obstruction. One of these patients (No. 1) improved radiographically during cord stimulation and voided at a lower detrusor pressure and at an increased rate (fig. 2). Eleven patients (all except Nos. 4, 5, 6, 9, 10) were considered to have detrusor sphincter dyssynergia on the basis of intermittent involuntary dissociation between flow rate and micturition pressure with corresponding sphincter contraction seen on x-ray and on sphincter electromyography, or failure of sphincter relaxation in the presence of adequate detrusor contraction. Four of these patients (Nos. 1, 8, 13, 16) showed improvement and sustained sphincter relaxation whilst voiding during cord stimulation.

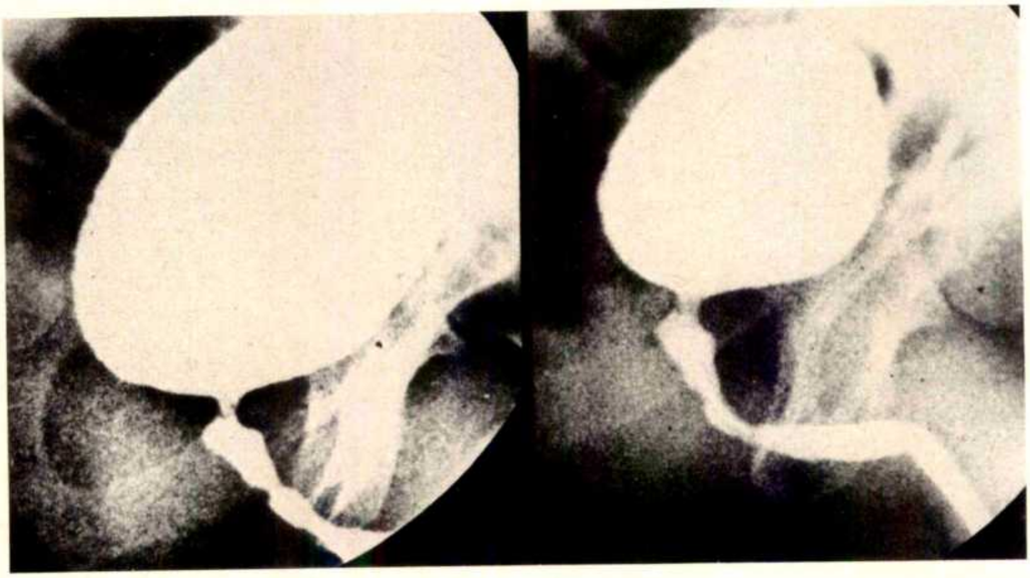

FIG. 2. Representative frames from micturating cineurethrocystograms (Patient No. 1) performed before (*left*) and after (*right*) two weeks' cord stimulation. Opening of the bladder neck during stimulation is shown.

(v) Sphincter electromyography: satisfactory recordings were obtained from the external urethral sphincter in 11 of the patients (all except Nos. 1, 4, 5, 6, 13). It is generally accepted that after an initial burst of insertion activity, electrical silence is the commonest finding in the normal external urethral sphincter (Petersen and Franksson, 1955; Allert and Jelasic, 1968, 1970). The abnormality seen in our 11 patients was continous prolonged activity lasting for several minutes following electrode insertion and sometimes for the entire duration of the examination (fig. 3). This abnormal activity was abolished in 3 patients (Nos. 8, 15, 16).

C. *Mictiograph Results*

These are set out in Table 5. The apparatus was not available for Patients 3, 4, 5 and 6. As can be seen, the only significant improvement in urinary flow occurred in Patient No. 1 though all the others showed a similar but much slighter trend. Fig. 4 shows representative tracings from Patient 1 before cord stimulation and fig. 5 representative tracings from the same patient during the second week of cord stimulation. The 'temporary' electrodes were kept *in situ* in this patient for ten

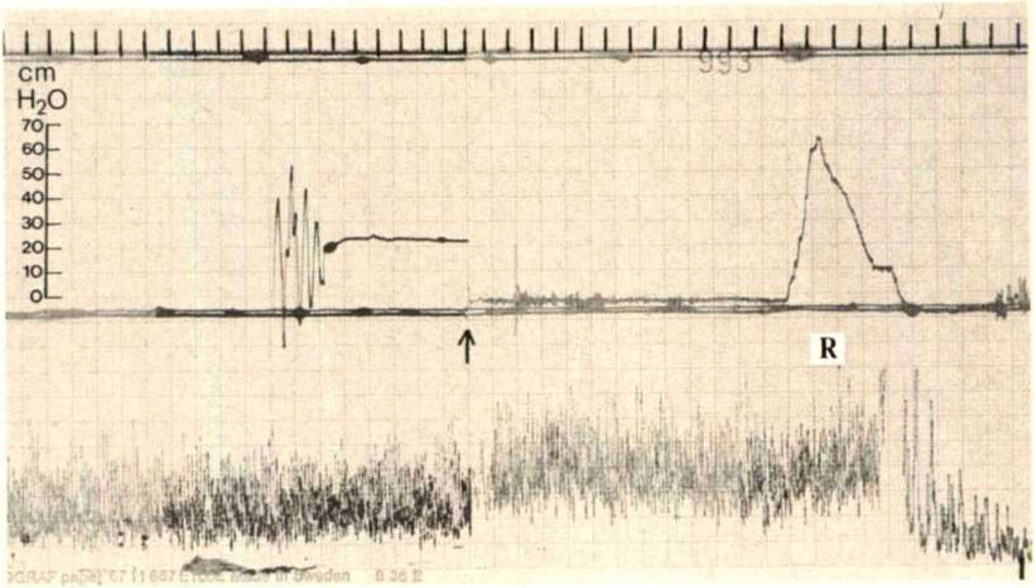

FIG. 3. Photograph of urethral pressure profile trace (taken before cord stimulation) to show continuous activity of external urethral sphincter on bottom line (EMG input passed through a leaky integrator). The coaxial needle had been inserted 20 min prior to this section of the record and activity continued, in this patient, unabated for the 90 min of the examination. The middle line shows a urethral pressure curve at rest (R) with preliminary adjustments. The Porges catheter is withdrawn commencing at the point marked with an arrow with the patient asked to relax. An increase in sphincter activity indicated by a rise in the mean baseline can be seen during withdrawal. Time marker (at top of record) at 1 s intervals. There was no rectal pressure line in this patient who had had a total colectomy for ulcerative colitis.

TABLE 5. AVERAGED FLOW DATA OBTAINED FROM DAILY MICTIOGRAPH RECORDINGS

	Average volume per void (ml)		*Average time per void (s)*		*Average flow rate (ml/s)*		*Maximum flow rate (ml/s)*		*Flow 'peaks'**	
Patient	*Before*	*During*	*Before*	*During*	*Before*	*During*	*Before*	*During*	*Before*	*During*
1	356	356	71	26	5.0	15.0	16	22.5	5	1
2	66	98	47	42	1.5	2.7	6.9	11.0	3.5	3
7	318	317	78	74	4.2	4.4	11.9	10.7	4.5	3.8
9	156	194	40	44	3.7	4.0	8.8	9.6	1.6	1.1
10	268	273	60	49	4.7	5.7	13.4	13.3	4.0	1.8
11	180	167	82	65	3.7	4.2	8.1	10.6	2.8	2.2
12	106	119	62	45	1.9	2.8	5.4	8.3	4.9	3.0
16	86	187	21	23.6	4.2	8.1	10.2	13.8	1.3	1.3

* Interrupted periods of urine flow during each void—*see* fig. 4 for examples. Only patients able to perform the test before and during cord stimulation are shown.

weeks, during which time this considerable improvement was maintained. During the third week of cord stimulation, and while the patient was still in hospital, the stimulation was reduced to just below the threshold at which paræsthesiæ occurred. An apparent 'dose-related' response was obtained as shown in fig. 6.

The changes in flow pattern took the form of increases in both maximum and average rates of flow and a reduction in the time taken for each act of micturition in which there was also a reduction in the number of interruptions, that is, fewer flow 'peaks' per act of micturition (*see* fig. 4).

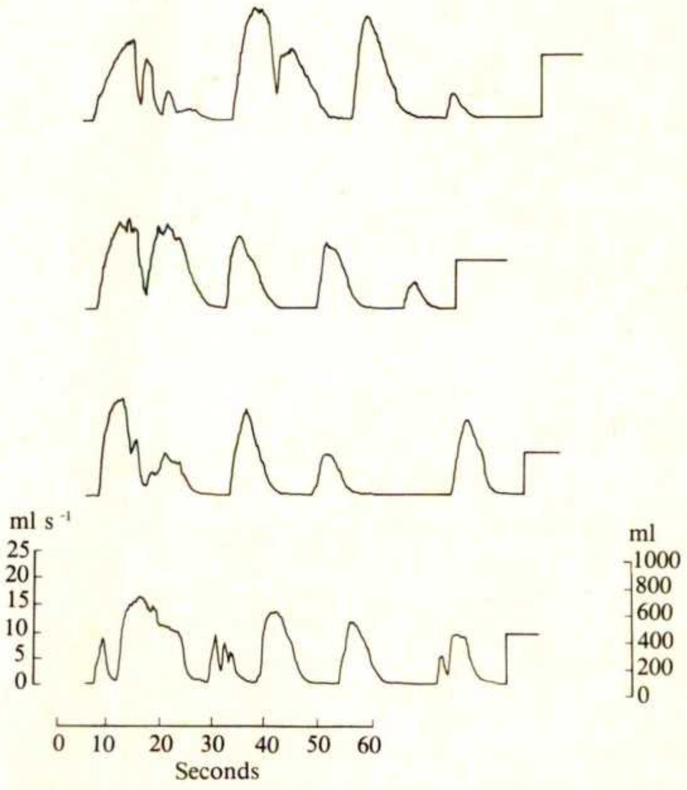

FIG. 4. Sample prestimulation mictiograph tracings from Patient 1 showing interrupted flow pattern giving a multipeaked tracing and prolonged voiding time. Horizontal bar at end of trace indicates total volume voided according to scale on right hand side. Time along abscissæ in seconds. Flow rate on left hand scale in ml s^{-1}.

6. *Miscellaneous*

One patient had had continuous deep burning pain in both legs and lower back for two to three years prior to cord stimulation. This was abolished overnight and did not return until four weeks after the electrodes were removed. A further patient had similar pain in the region of the right hip—this was also abolished for the duration of cord stimulation and did not return for eight weeks after electrode withdrawal. No consistent pattern of change in foot skin temperature was noted.

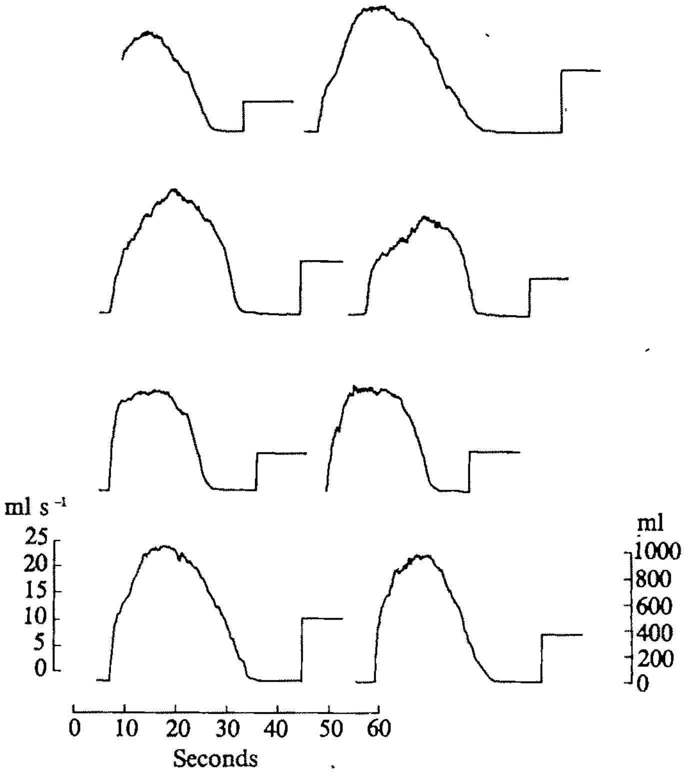

FIG. 5. Sample mictiograph tracings from Patient 1 during second week of cord stimulation, showing uninterrupted flow pattern and normal voiding time. Conventions as in fig. 4.

7. *Subjective Impressions*

Only 2 patients (Nos. 6, 10) in the original group of 11 denied overall improvement though both had, in fact, slightly reduced their walking times. One had decreased lower limb spasticity and improved bladder function (No. 6). The other patient's pessimism was reflected in the objective tests.

The remaining 9 patients all claimed improvement of varying degrees in varying functions often in the face of deteriorating objective evidence. Almost all these claimed improvement in balance, agility, ability to stand without support and some claimed improved upper limb function especially for feeding. A non-specific feeling of wellbeing was also frequently mentioned, as was absence of nocturnal flexor spasms during cord stimulation.

8. *Electrophysiology*

(i) Somatosensory evoked potentials: all 9 patients in whom SEP were recorded showed abnormalities before treatment, in most absence of N13 with preservation of N9. When the serial records were assessed without knowledge of the relationship

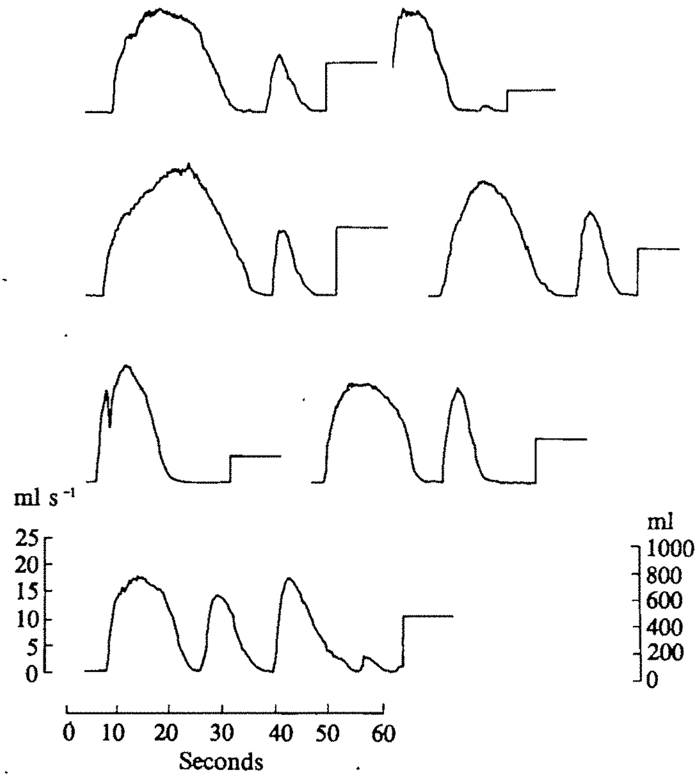

FIG. 6. Flow sequence over one day during third week of cord stimulation (Patient 1). Pattern intermediate between those shown in figs. 4 and 5. Stimulation at sub-threshold for paræsthesiæ. Conventions as in fig. 4.

to treatment it was not possible to detect any consistent pattern of change. In 5 patients there was no change; in 2 the potentials were more abnormal and in 2 rather less abnormal during cord stimulation (figs. 8, 9).

(ii) Electromyography: clinically, in the thin patients, the rectus abdominis could be seen to twitch rhythmically at a rate which seemed to correspond to the stimulation frequency, at least at the lower frequencies (7 to 20 Hz). In those patients who could induce spasticity in the legs by increasing the stimulation voltage without undue discomfort, a similar but less marked assocation with varying frequencies was also seen. Interestingly, this phenomenon always occurred first (or only) in the more seriously affected leg.

The findings in the 3 patients were similar. Contractions of the rectus abdominis occurred at the same frequency as that of cord stimulation at frequencies varying between 7 and 120 Hz (fig. 10) and occurred at 'normal' stimulation voltages.

The illustrations are taken from Case 10 where the stimulation voltage was subthreshold for paræsthesiæ. Despite this, the higher frequencies of stimulation were uncomfortable and at 120 Hz could only be tolerated for a few seconds.

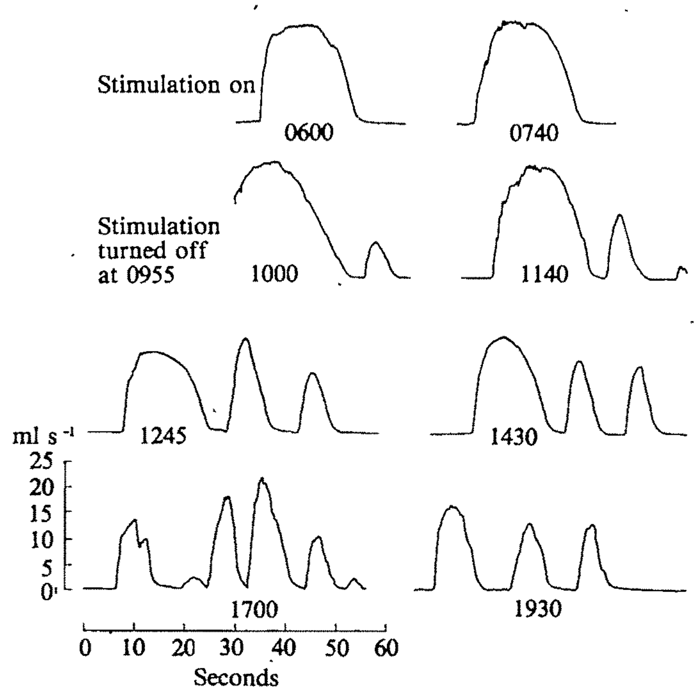

FIG. 7. Flow sequence over one day during third week of cord stimulation (Patient No. 1) with stimulator switched off at 0955 h. Gradual return to prestimulation pattern shown. Volume bars at end of each trace have been omitted.

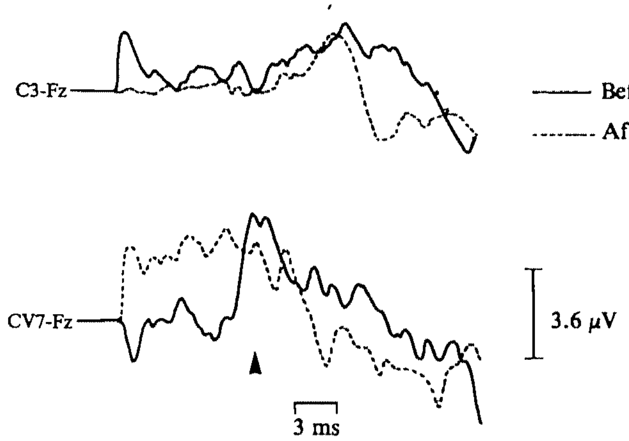

FIG. 8. Superimposed cervical and cortical potentials evoked by stimulation of the right median nerve at the wrist (Patient No. 8) before (solid line) and during (dotted line) cord stimulation. A recognizable N13 (marked by arrow) is abolished during stimulation. In this and the subsequent figure, the cortical potential was recorded from an electrode placed approximately over the hand area of the left sensory cortex (C3); and the cervical potential (CV7) from an electrode placed in the midline over the 7th cervical spinous process. Both were referred to a frontal reference electrode (Fz; 10-20 system).

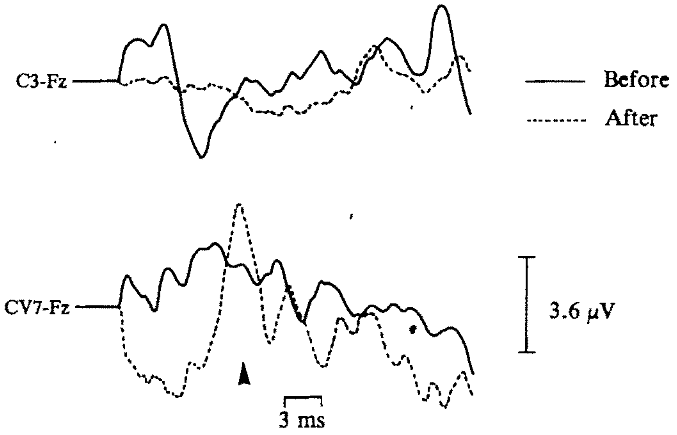

FIG. 9. Superimposed cervical and cortical potentials evoked by stimulation of the right median nerve at the wrist (Patient No. 2) before (solid line) and during (dotted line) cord stimulation. A recognizable NT3 (marked by arrow) appears during cord stimulation, though this was not reproducible.

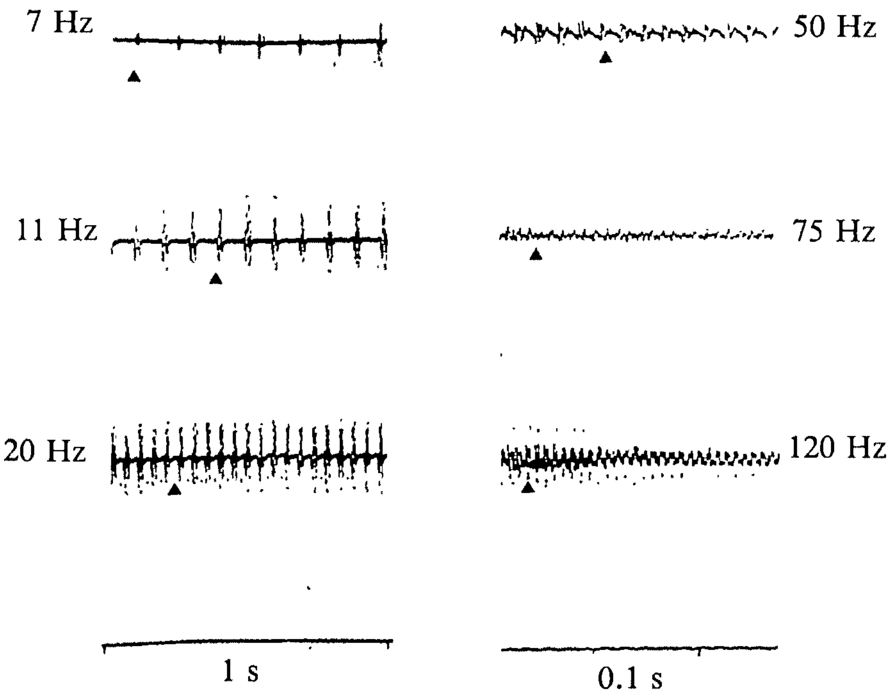

FIG. 10. EMG of right rectus abdominis. *See* text for explanation. Time scales applicable to columns above; arrows indicate spinal stimulator artefact.

Recordings from the thigh muscles at the 'normal' 33 Hz with the voltage gradually increased to beyond comfortable levels (fig. 11) demonstrate twitches in the biceps femoris at 33 Hz with an occasional twitch in the quadriceps until at an uncomfortable level of stimulation both muscles contract tetanically. In one patient (No. 1) recordings from the thigh muscles were made at different cord stimulation frequencies and at a voltage level 0.5 V above the threshold for paræsthesiæ (not illustrated). Simultaneous hamstring/quadriceps twitches were recorded at the following frequencies:

Cord stimulation frequency (Hz)	7	10	20	33
Muscle twitch frequency (Hz)	7	10	10	8

The last was painful and the frequency was not increased further.

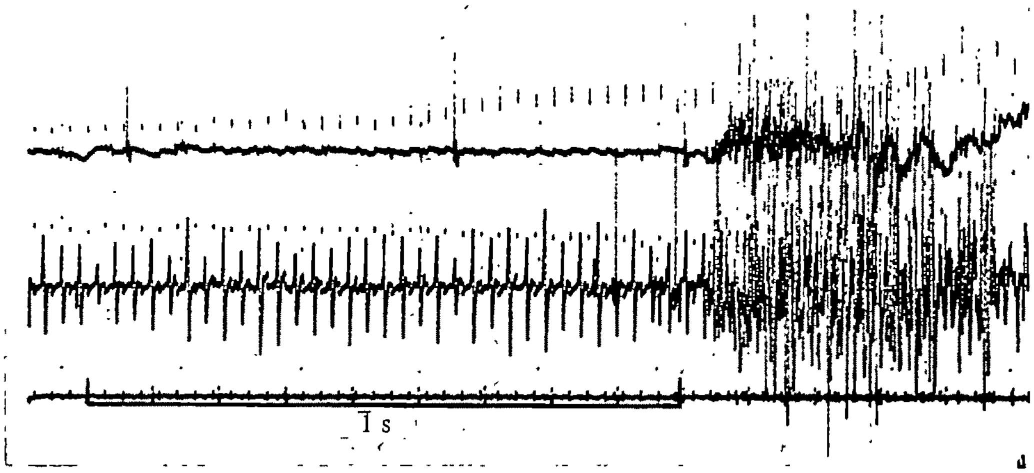

FIG. 11. EMG tracings from quadriceps femoris (*upper trace*) and biceps femoris (*lower trace*). For explanation *see* text. Spinal stimulator artefact appears on top trace (*cf.* fig. 10).

(iii) Applied current measurements: there were large variations in current and voltage required to produce paræsthesiæ in the legs (Table 6). Although the assumptions used in making the calculations are likely to produce some inaccuracies especially where the inter-electrode resistance is small, at least an approximate idea of the values is obtained. The distribution of all three electrical values in those patients whose bladders (Nos. 1, 8, 13, 14, 15, 16) or leg spasticity (Nos. 1, 2, 5, 6, 7, 9, 12, 14, 15) improved was, in fact, random though there is a suggestion that those whose bladders improved clustered at the lower end of the resistance and voltage ranges.

TABLE 6. DETAILS OF APPLIED VOLTAGE, CALCULATED CURRENT AND INTERELECTRODE RESISTANCE VALUES, AND ELECTRODE SEPARATION AND PLACEMENT

Patient	*V*	*mA*	*Ω*	*Electrode position*	*Electrode separation (cm)*
1	5	10	500	D9–10	3
2	2.5	4	625	D5–7	6
3	7.5	4.8	1560	D2–4	5
4	2.2	2.1	1050	D3–4	4
5	4.5	4.4	1020	D3–5	6.5
6	12.5	7.5	1670	D2–3	2
7	12.5	9	1390	D7–8	2.5
8	0.1	0.4	250	D7–9	4.5
9	4	3	1330	D3–5	3
10	4	7.4	540	D10–12	8.5
11	4	2.6	1540	D4–5	3
12	3	4	750	D9–10	2.5
13	0.9	2.8	320	D6–8	5.5
14	8	15	530	D6–7	5
15	4.5	5.2	860	D9–10	2
16	4	6.2	640	D3–4	4

DISCUSSION

Although six years have elapsed since the original observation (Cook and Weinstein, 1973) of the effect of cord stimulation on neurological function, there is very little published evidence outside specialized symposia (Proceedings of the 6th International Symposium on External Control of Human Extremities, 1978). In two large series available, the claimed success rates were high. Cook (1976) reporting his experience of 'more than 70 patients' claimed 'substantial improvement in at least 90 per cent of patients treated'. No details were given of the patients' disabilities, the methods and frequency of testing (other than an initial formal neurological examination) or the results of such tests as may have been performed. Dooley (1977) claimed an overall success rate of 76 per cent (32 out of 42 patients) and gave a little more detail concerning bladder function, but again published no details of any objective assessment. Illis *et al.* (1976) reporting on two patients carefully studied confirmed the original clinical observations and produced neurophysiological evidence of a change in central nervous system function due to cord stimulation.

At a recent symposium (Proceedings of the 6th International Symposium on External Control of Human Extremities, 1978) a total of 7 centres, 2 from the United Kingdom and 5 from the USA, reported their experience with cord stimulation in multiple sclerosis. The American centres with series ranging from 8 to 63 patients all claimed success rates varying between 60 and 100 per cent, one paper

(Davis *et al.*, 1978) claiming a '20 to 30 per cent improvement in all modalities' in all 63 patients treated. None of these papers gave any details of the neurological changes sufficient for an independent assessment of whether or not the stated conclusions of improvement could be supported by the evidence produced. One paper (Dooley *et al.*, 1978) did give some detail of changes in bladder function but this was inadequate for critical analysis. Cerebellar ataxia, brain-stem function and visual disturbances were all reported to improve.

Of the two British centres, Illis, Sedgwick and Tallis (1978) reported on 12 patients, all of whom were assessed on the Kurtzke scale. An attempt was made in 3 of these patients to exclude a placebo effect by using surface stimulation for three days, and in a further 2 patients with the batteries removed from an otherwise fully operational system. The overall success rate in this series was lower than in the others. Pyramidal and sensory functions both improved in a third of the patients while cerebellar dysfunction did not improve at all. This work was subsequently extended (Illis *et al.*, 1980) to include another 7 patients with similar results. Seven out of 8 patients showed improved amplitude of the cervical SEP and 3 out of 10 a decreased brain-stem evoked potential latency. Visual evoked responses and contingent negative variation did not alter in the same group of patients (Sedgwick *et al.*, 1980).

The contribution by Hawkes *et al.* (1978) was even less encouraging. This was a preliminary report of 21 patients, 19 of whom were chosen for the subsequently published report (Hawkes, Wyke, Desmond, Bultitude and Kanegaonkar, 1980). Patients were assessed clinically, by videotape recording, psychomotor testing and a full range of urodynamic studies in 14 patients. Muscle tone was stated not to change. Any change seen other than in bladder function was minor and regarded as insignificant, being the result of familiarity with tests and training at them over the course of the stimulation period. Only questionable changes were obtained in the cervical SEP in a few of the patients.

Since this study was completed, the only two papers to date reporting no improvement in MS from cord stimulation have been published. Rosen and Barsoum (1979) found no improvement at all on objective criteria in a group of 9 patients with static MS, although 30 per cent of these claimed subjective benefit which was ascribed to the placebo effect. No attempt was made to screen patients temporarily before implanting a permanent stimulator and the tests performed would not have been capable of detecting such changes as can occur. Their conclusion that cord stimulation can no longer be recommended for MS must be interpreted with caution. Young and Goodman (1979) studied 23 patients with MS, basing assessment on the Kurtzke scale with the addition of specific quantifiable tests of walking speed, sensation and visuomotor co-ordination. Objectively, no significant improvement was found in any function though 30 per cent of the patients claimed subjective improvement. No specific mention was made of spasticity and sphincter function was assessed clinically, cystometry being performed in only 11 patients. Apart from the bladder assessment, this paper shows evidence of careful and objective analysis and agrees with both the present findings and those of Hawkes *et al.* (1980) in being unable to recommend the treatment primarily for complaints other than those of bladder dysfunction.

Unlike the effects of cord stimulation on other disordered neurological function in MS, there appears to be a much greater degree of agreement between the various interested groups on its effect on the urinary bladder. All the published favourable reports cited in this paper, except Cook and Weinstein's original 1973 paper, claim improvement in bladder function in from 30 to 100 per cent of patients, but again with little objective supporting data, other than that in the paper by Hawkes *et al.* (1980).

Dooley (1977) and Dooley *et al.* (1978) described the results of cord stimulation in 38 patients with neurogenic bladder dysfunction due to MS. All 7 with (undefined) 'hypotonic' bladders improved with 'at least 50 per cent reduction in frequency and incontinence' of whom 3 had reductions in residual volumes from > 100 ml to < 80 ml. The remaining 31 were classified, again on undefined criteria, as having 'hypertonic' bladders and of these only 5 improved, the improvement being described as 'better control of urination'. In 4 of those 5, decreases in residual volume were recorded and in the fifth an increase. Seven of the 12 patients who improved had between one and five daily episodes of incontinence which were abolished by cord stimulation.

Tallis *et al.* (1978) reported their experience of 11 patients of whom 8 were incontinent (5 continuously and 3 intermittently). Cystometry was carried out on 6 patients but unfortunately this did not include any who claimed significant subjective improvement. Based on Kurtzke's bladder dysfunction scale, 6 of the patients showed an improvement of one or two grades. Symptomatically frequency was markedly reduced in 4 and slightly in one of the 11, urgency markedly in 2 and slightly in 5 of the 8 patients with this symptom, and incontinence improved slightly in 2 and markedly in 4 of the 8. Five of the patients had detrusor hyperreflexia and one detrusor areflexia. One further patient, although complaining of frequency, urgency and hesitancy, surprisingly had a normal cystometrogram. Two of these patients had improved cystometrograms manifest as an increased filling capacity.

Hawkes *et al.* (1978) in a preliminary report on 21 patients found symptomatic improvement in hesitancy and urgency in two-thirds of the patients with a statistically significant improvement in urinary volume/time ratios (Hawkes, 1979) in a similar proportion. In the 14 patients studied in detail (Hawkes *et al.*, 1980) urodynamic findings were qualitatively similar to those described here: 13 patients exhibited detrusor hyperreflexia; during stimulation 2 of these showed a significant decrease in detrusor instability; dyssynergia improved in one; maximum urethral closure pressure decreased in 5 out of 7 patients, and 2 out of 5 assessed with the mictiograph showed increased flow rates.

Abbate, Cook and Atallah (1977) dealt exclusively with the effects of cord stimulation on the bladder. Details of individual patients were not given and urodynamic testing was not carried out on all the patients. Subjective improvement was found in 31 of their 40 patients but objective confirmation of this in only a percentage (42.5 per cent), representing an indeterminate number of patients. Detrusor hyperreflexia improved by 'increasing bladder capacity and improved sphincter control with resulting continence' and detrusor areflexia by 'varying degrees of decreased bladder capacity and residual urine and improvement in proprioception and sphincter control'.

In 2 of the 12 of our patients in the present series, who claimed subjective improvement, objective urodynamic support for the improvement was lacking. This, and the subjective assessment of reduced frequency, not corroborated by the output charts in most of our patients, underlines the need for caution in the interpretation of any conclusions based mainly or entirely on subjective data. Therapeutic trials in MS are notoriously difficult and a double blind protocol cannot be used to assess the results of cord stimulation. We chose only patients with static or slowly progressive disease who had had no major fluctuations in their condition for at least a year, in an attempt to avoid confusion with natural variations. Although the objective of cord stimulation was to improve the quality of life, as far as possible assessment was based on variables that could be measured. Tests were kept to a minimum to avoid any effect of fatigue. The videotaping, and subsequent assessment by an independent panel of observers, of selected activities could not be quantified but were scored without knowledge of the treatment states of the patient. Changes in SEP were also assessed 'blind'. The results of all these tests have also to be interpreted against the background of the often exaggerated expectations of highly motivated patients who put great efforts and determination into trying to make the treatment work (Poser, 1979).

Voluntary reduction of spasticity in MS must be regarded as almost impossible. We were impressed by the remarkable decrease in leg spasticity in some of our patients; the lesser degree of reduction in others (and the frequent reports of abolition of nocturnal flexor spasms), especially as this occurred with no reduction in voluntary power, seems therefore to be a genuine accompaniment of cord stimulation. This phenomenon was also reported in a group of six patients with traumatic paraplegia all of whom obtained reduction in lower limb spasticity as well as autonomic effects such as piloerection, sweating, penile erection and increased lower limb skin temperature (Richardson, Cerullo, McLone, Gutierrez and Lewis, 1979). Spasticity did, however, increase in two patients but without knowledge of the exact mode of action of stimulation any explanation for this would be highly speculative. Apart from the paper by Richardson *et al.* (1979), which did not deal with MS, there is no mention, in any of the publications on cord stimulation in MS, of a reduction in leg spasticity, which was a notable feature in the patients reported here. No other change in limb function was sufficiently pronounced to convince us that it was the result of anything but a combination of enthusiasm, training and prolonged individual medical attention.

The electrophysiological studies were necessarily limited and at present throw no light on the mode of action of cord stimulation, other than to suggest that the influence of the applied current in humans extends beyond the dorsal columns, previously thought to be the major site of stimulation (Nashold and Friedman, 1972; Illis *et al.*, 1978), though Bantli, Bloedel, Long and Thienprasit (1975) had shown that in the Rhesus monkey, cord stimulation parameters in clinical use activated most ascending and descending pathways either directly or trans-synaptically. Cord stimulation in our patients had little or no effect on the disordered SEP and was as likely to be associated with deterioration (*cf.* Blair, Lee and Vanderlinden, 1974) as with improvement. Sedgwick *et al.* (1980) found improvement in the SEP in 7 out of 8 patients and in some this extended to the appearance of a virtually normal N13 from a previously abnormal potential. We, like Hawkes *et al.* (1978), were unable to confirm this.

In the absence of any detailed knowledge of the mechanism of action of cord stimulation, the values of current requirement (and indeed the arbitrary choice of frequency) have little practical value at present. It could be argued, however, that the higher values of inter-electrode resistance might be associated with more extensive plaque formation and therefore with less likelihood of benefit, though there were exceptions even to this (*see* Patients 6, 7, 9).

In a different category were the tests of bladder function. Unlike functions over which voluntary control can be exerted, the nature and consistency of the objective changes in bladder function observed in these patients are such as to preclude any significant placebo element. In support of this conclusion is the 'dose-related' response of one of our patients to sub-threshold levels of stimulation (fig. 6) and the 'decay curve' of his improvement when the stimulation was switched off (fig. 7).

Objectively measurable changes in bladder function in our patients took the form of increased bladder capacities (as found by Tallis *et al.*, 1978); voiding at a lower detrusor pressure; and, in all but two, reduction in the maximum urethral closure pressure as found by Hawkes *et al.* (1980) in some of their patients.

The maximum urethral closure pressure has both an active component, which reflects striated and smooth muscle activity, and a passive component, which depends on the elastic properties of the urethra and support given to it by the surrounding vascular connective tissue. It is possible that cord stimulation alters the striated muscular activity of the urethra by reflex inhibition (*vide infra*) but there was evidence of improvement of sphincter dyssynergia in only 4 of 11 patients despite a reduction in maximum urethral closure pressure. Cord stimulation produced objectively 'better voiding' in a further 3 patients, all of whom again showed a significant reduction in maximum urethral closure pressure but in only one of whom there was evidence of radiologically improved bladder neck/urethral opening (fig. 2).

One possible explanation would be an effect of cord stimulation on autonomic function, which can be considerable (Nashold, Friedman, Glenn, Grimes, Barry and Avery, 1972; Richardson *et al.*, 1979). The urethral vascular cushion under autonomic control (Tanagho, Meyers and Smith, 1969) together with the sympathetically controlled urethral smooth muscle are thought to contribute the major part of the measured urethral pressure (Nordling, 1978) and alteration in these factors may account for the observed decrease in maximum urethral closure pressure in the presence of qualitatively unchanged tonic contraction of the external sphincter.

Uninhibited detrusor contractions were abolished in only one patient (No. 16), though others did show a reduction in the amplitude of the contractions, a phenomenon easiest to explain by reflex inhibition. Urodynamic assessment records function at one particular time and with the added factor of multiple catheterizations, possibly inducing local irritative reflexes (Bors and Blinn, 1957). A truer picture may be inferred from the averaged daily flow readings obtained on the mictiograph which suggest that flow rates are increased in the majority of the patients. Our results indicate that the effects of cord stimulation in MS, with the exception of bladder function and to a lesser degree lower limb spasticity, are not as encouraging as was first reported. We have not studied the effect of permanently implanted electrodes but there is considerable evidence (Dooley (1977) and various authors in Proceedings of the 6th International Symposium on External Control of Human Extremities, 1978) that any improvement takes place in the first few days of cord stimulation and that in those who do not improve initially, long term stimulation is not beneficial (Hawkes, 1979; Rosen and Barsoum, 1979; Young and Goodman, 1979). We have, because of worthwhile bladder function improvement, kept the temporary percutaneous systems in place in seven patients for four to twenty weeks and in none did any further improvement occur. Our results can therefore be compared with other published series that include permanent implants but which do not otherwise differ in technique or stimulation characteristics. Ten of our patients had electrodes placed lower in the spinal canal than is customary. These were all later in the series and this was done in an attempt to produce better bladder results. All but one of our patients who produced the most gratifying bladder improvement were in this category.

Most of the centres actively involved in using cord stimulation as an experimental symptomatic treatment are agreed that improvement can be produced in patients with MS. There is, however, a serious need for more extensive use of objective criteria. Based on subjective impressions only, the claimed success rate in this series would have been closer to 75 per cent for most functions instead of the very low level actually recorded. Despite our belief that cord stimulation is likely to be of limited value, it has undoubted effects which cannot be explained on a placebo basis. The two most important are on urinary bladder dysfunction and on spasticity. Both these effects could result from the inhibition of excessive spinal reflex activity.

There is now a large body of evidence in support of Hughlings Jackson's 1887 hypothesis that the main neurophysiological change at spinal cord level due to damage to pathways at a higher level is a result of interruption of descending inhibitory influences. This was also the conclusion reached by Denny-Brown and Robertson as a result of their painstaking studies of bladder physiology, both in the normal subject (1933*a*) and in three cases of traumatic complete lesions of the spinal cord above the sacral segments (1933*b*), neatly summarized thus: 'The reactions of the bladder mediated by the vesical plexus and sacral segments of the spinal cord differ from those of the normal bladder only in lack of appropriate restraint'. Similar findings were obtained by Langworthy and Lewis (1935) in two patients with MS.

We have shown that at stimulation voltages considered 'normal' by the patient, and even at those sub-threshold for paræsthesiæ, it is possible to record direct muscle responses at the frequency of cord stimulation (between 7 and 120 Hz) due either to direct excitation of the anterior horn cells or to stimulation of descending tracts, as the segmental origin of the thigh muscles involved (L2–S2) was, in one case, well below the level of the epidural electrodes (D7–D8 vertebral level, approximate cord level D9–D11). This suggests that the entire spinal cord in the region of the electrodes is influenced by the applied current and it is tempting to postulate that descending inhibitory pathways below the level of maximum occurrence of MS plaques in the cervical cord are stimulated. Such a 'barrage' pattern of continuous and quite unphysiological descending inhibition might be expected to depress local reflexes from both voluntary muscle and the bladder and hence give rise to the improvements seen. This pattern of artificial inhibition would not be expected to return disordered function to complete normality and indeed this is not seen. It is interesting that resolution towards normal of a previously 'spastic' H reflex recovery curve was one of the neurophysiological changes recorded in one of Illis *et al.*'s first patients (Illis *et al.*, 1976). Also of note are the experiments of Siegfried, Krainick, Haas, Adorjani, Meier and Thoden (1978) on decerebrate cats, in which cord stimulation (50 Hz, 200 μs duration, 0.1 mA) at various thoracic levels for between 1 and 30 s caused prolonged reduction (up to 10 min) of monosynaptic reflexes, reduced firing frequency of motorneurons and increased Renshaw cell firing at lumbar levels.

Another quite different hypothesis can be constructed on the basis of the experiments on dorsal horn cells in the spinal cat performed by Iggo and his colleagues (Iggo, 1978). They found a class of neurons responsive to both nociceptive and cutaneous mechanoreceptor afferents. Noxiously-induced persistent discharge of the neurons could be inhibited by afferent input from the mechanoreceptors and this effect could be mimicked by electrical stimulation of the dorsal columns, stimulus frequencies between 10 and 50 Hz being sufficient to cause almost complete suppression of the neurons. This was suggested as a possible explanation for the pain-relieving properties of cord stimulation. Earlier work by Dimitrijevic and Nathan (1967) had shown that in paraplegic man, spasticity was to some extent dependent on afferent stimuli and that reduction of this input by blocking large cutaneous nerves in the legs, or occluding lower limb circulation with a cuff, reduced spasticity.

The relationship between a full bladder and increased lower limb spasticity with a reduction following the emptying of the bladder is a well recognized clinical phenomenon, and has been confirmed electrophysiologically (Dimitrijevic and

Nathan, 1967; Mai and Pedersen, 1976). Bors, Rossier and Sullivan (1962) had shown that anæsthetizing the bladder mucosa has a similar effect in reducing lower limb spasticity to that of blocking large cutaneous afferent nerves and occluding the circulation to one leg.

It was first shown by Gros, Ovaknine, Vlahovitch and Frerebeau (1967) that selective posterior rhizotomy performed for relief of spasticity may also have a beneficial effect on urinary function. This had been suggested ten years earlier by Bors and Blinn (1957) who also demonstrated that prolonged amelioration of bladder dysfunction in some patients with traumatic paraplegia (and one with spinal MS) could be obtained by instilling local anæsthetic into the bladder. Temporary alleviation of symptoms was said to occur in half of the 115 patients studied, with increases in bladder capacity and reduction in residual volume. They examined the effect of mucosal anæsthesia on the bulbocavernosus reflex as recorded from the sphincter ani, and found the response to the usual provocative stimuli and to instillation of ice water into the bladder and pulling on the indwelling Foley catheter to be reduced or abolished.

All these manœuvres reduce input to the spinal cord and on Iggo's hypothesis, cord stimulation could therefore be looked on as yet another means of reducing input to the spinal cord in the same way as blocking afferent nerves, anæsthetizing the bladder mucosa and cutting posterior roots, thereby damping the hyperexcitable reflex arcs responsible for the clinical picture of detrusor hyperreflexia with sphincter dyssynergia and lower limb spasticity.

Bladder dysfunction is a very common feature of MS and this is not surprising as the reticulospinal tracts concerned with higher control of the spinal micturition reflex centres (Nathan and Smith, 1958) are commonly included in the plaques of demyelination in the lateral white columns (Fog, 1950; Oppenheimer, 1978). The neural control of the bladder is highly complex, still imperfectly understood and depends on the smooth integration of a large number of sacral reflexes, some inhibitory and others facilitatory (Kuru, 1965). The disruption of this integrated control by a random scattering of MS plaques is likely to produce a state impossible to remedy even partly by the artificial 'blanket' replacement of ascending and descending impulses which almost certainly include facilitatory as well as the inhibitory influences we have discussed. We are aware that facilitation of some of the micturition reflexes may take place (for example, in the four patients who showed sphincter relaxation during voiding, having previously exhibited detrusor/sphincter dyssynergia) but the majority of the objective changes seen, both in the limbs and in the bladder, are better explained by increased descending inhibition.

The purpose of cord stimulation is not to improve some measurable but irrelevant quantity but to improve the quality of life. We have succeeded in doing this in only six of our patients to date, in all of whom improvement in bladder function enabled them to lead more normal lives for the four to twelve weeks that their temporary percutaneous electrodes remained in position. In two of these patients a marked decrease in lower limb spasticity also enabled them to be considerably more mobile.

In several other patients a lesser degree of sphincter control or a reduction in leg spasticity made life a great deal more pleasant which, if sustained with later permanent implantation, would have a considerable effect on the quality of their life.

SUMMARY

Eleven patients with static or slowly progressive multiple sclerosis were treated with continuous spinal cord stimulation *via* epidural electrodes for a minimum of two weeks. An extensive battery of objective tests was used to assess results. Significant improvement in urinary bladder function was seen in 2 of the patients with a lesser degree of improvement in 4 others and reduction of lower limb spasticity in 6 patients. Five additional patients selected for these disabilities were then treated with further evidence of improvement in bladder function in 4 and in lower limb spasticity in 2. It is suggested that benefit results from inhibition of excessive spinal reflex activity.

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PARÆSTHESIÆ FROM ECTOPIC IMPULSE GENERATION IN HUMAN SENSORY NERVES

by JOSÉ L. OCHOA *and* H. ERIK TOREBJÖRK

(From the Division of Neurology, Dartmouth Medical School, Hanover,
New Hampshire 03755, USA, and the Department of Clinical Neurophysiology,
University Hospital, 750 14 Uppsala, Sweden)

INTRODUCTION

THE pathophysiological basis for paræsthesiæ from peripheral nerve dysfunction has remained speculative for powerful reasons. A favourite hypothesis implicates the spontaneous generation of impulses from within the 'sensory unit' (Lewis, Pickering and Rothschild, 1931; Zotterman, 1933; Kugelberg, 1944; Weddell and Sinclair, 1947; Gordon, 1948; Merrington and Nathan, 1949). As defined by Sarah Tower (1940) such a unit, composed of a single afferent fibre together with its terminals, cell body and central processes 'could be considered as the sensory equivalent of the neuro-motor unit'. Thus, paræsthesiæ would be the sensory equivalent of spontaneous motor unit discharges known to underly fasciculation, myokymia, tetany, etc.: such discharges from individual motor units can be conveniently recorded from the muscle effector with ordinary needle electrodes. Any inquiry into single sensory unit activity presupposes the ability to record directly, with intraneural microelectrodes, from sensory nerve fibres. Further, any attempt at correlating the afferent messages with sensory experience requires the recording of afferent nerve impulses in awake human subjects. Vallbo and Hagbarth (1968) introduced the microneurographic technique that meets those prerequisites. Here we report on spontaneous discharges in sensory fibres, recorded with this technique, from awake subjects actually experiencing paræsthesiæ. Preliminary results have been published elsewhere (Torebjörk, Ochoa and McCann, 1979).

METHODS

General Procedure

The investigation was carried out at room temperature on three normal subjects, ranging in age from 40 to 50 years. They lay relaxed on a couch with the arm comfortably supported. Lacquer-insulated tungsten semi-microelectrodes were inserted manually into the nerve to be explored. In order to provoke post-ischæmic paræsthesiæ, a 12 cm wide sphygmanometer cuff was inflated to 220 mm Hg and maintained for 10–20 min at the level of the upper arm or for 20–30 min round the mid-forearm. Movements of the extremity were avoided. In some experiments hyperventilation was performed during the first five minutes after release of the cuff. The subjects were instructed to verbalize spontaneous sensory experience which was stored on tape simultaneously with recordings of neural signals from myelinated and unmyelinated fibres. The subjects had optional access to the neural signals being audiomonitored and displayed on an oscilloscope screen.

Recording Sites

Thirty recordings were made in sensory nerve fascicles of the median or ulnar nerves at wrist or elbow levels, below or above the cuff. As illustrated in fig. 6B, the sensory fascicles were identified by (a) afferent discharges evoked by tactile stimulation of the skin of the hand and (b), the occurrence of typical skin nerve sympathetic activity, which could be increased by various manœuvres that raised the attention of the subject (Hagbarth, Hallin, Hongell, Torebjörk and Wallin, 1972). Recordings from muscle fascicles or mixed fascicles supplying both muscle and skin were not included in this study.

Artefacts

While manipulating the recording electrode in search of suitable recording conditions, high frequency discharges might be triggered by mechanical injury to nerve fibres. However, change in recording electrode position was seldom required during the post-ischæmic period and, therefore, injury discharges are not likely to contaminate the present results.

Technical Details

The electrodes (diameter 0.2 mm, tip diameter 1-5 μm) and the recording and display systems are described in previous reports (Vallbo and Hagbarth, 1968; Hagbarth, Hongell, Hallin and Torebjörk, 1970). The signal-to-noise ratio was improved by the use of a 700-5000 Hz band pass filter and an amplitude discriminator. Signals distorted by filtering are not calibrated in the figures. An 'instantaneous' frequency plot, derived from the inverse of intervals between successive spikes, was used to measure the discharge frequency of individual units. An RC integrating network with a time constant of 0.1 s was used to obtain a mean voltage display of multi-unit activity.

Electrical stimulation was performed with a Grass S 48 stimulator delivering square wave pulses of 0.1 ms duration with amplitudes up to 100 V at a frequency of 0.3 Hz. Stainless steel needles were inserted intradermally at an interelectrode distance of 3 mm within the innervation zones of the impaled nerve fascicles and served as stimulating electrodes in the skin. In psychophysical experiments, painful electric pulses with a duration of 1 ms were delivered at a frequency of 1 Hz in trains of four impulses. The subjects were instructed to adjust the stimulus intensity to an arbitrary suprathreshold pain intensity level, and to readjust the stimulation intensity to this subjective level of pain in repeated tests before, during and after post-ischæmic paræsthesiæ.

Pulse plethysmogram was recorded by a Van Gogh light plethysmograph, Type ILP-7A. The photoelectric transducer was attached to the pulp of the fifth finger to indicate the return of blood supply on release of the cuff.

Temperature measurements were made by means of a thermocouple attached to the skin over the pulp of the fourth finger.

Electromyogram (EMG) was recorded with surface electrodes over the hypothenar muscles.

Local anæsthetic blocks. 1 per cent lidocaine was injected close to the ulnar nerve at elbow level or the digital nerves at the base of the index finger to produce complete anæsthesia in the distal innervation zone of the ulnar or median nerves.

RESULTS

Types of Paræsthesiæ and Multi-unit Neural Activity Following Release of Compression-ischæmia

It is only after the repeated experience of post-ischæmic paræsthesiæ and of the variations in their sequential emphasis that one comes to discriminate the various components of the sensory complex. Following the description by Merrington and Nathan (1949), we provisionally borrow their terminology.

A typical sequence of spontaneous neural activity correlating to various paræsthesiæ following the application of a cuff round the upper arm for twenty minutes, is illustrated in fig. 1. Intermittent paræsthesiæ, mainly referred to finger tips and described as '*tingling*' started about half a minute after release, and the neurogram showed an increase in neural activity with occasional bursts of impulses. 'Tingling' rapidly increased in frequency and intensity and evolved into high-frequency '*buzzing*' towards the end of the first minute. 'Buzzing' was perceived as an almost continuous vibration in multiple areas in fingers and hand. It peaked during the second minute and waned to disappear towards the third minute. During this period the over-all neural activity had reached maximum and was punctuated periodically by prolonged bursts of impulses (fig. 1A).

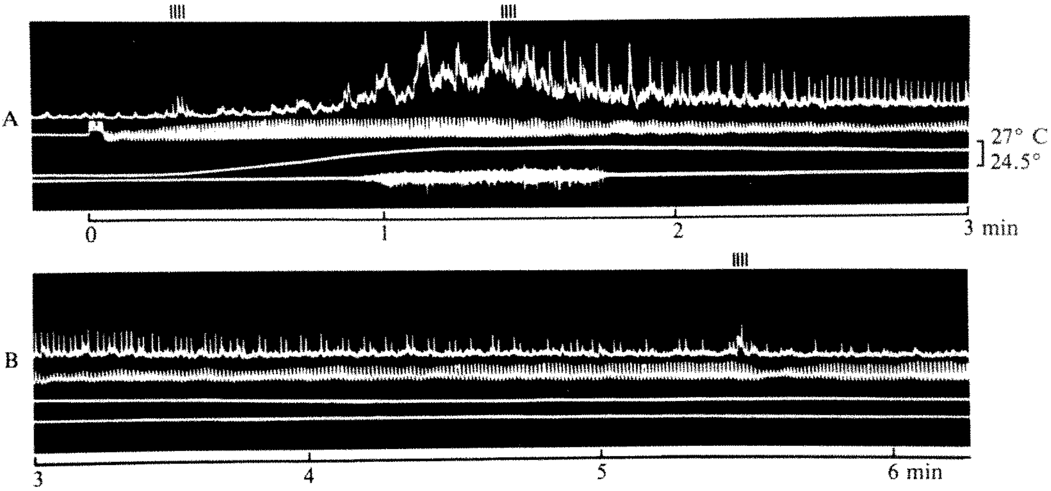

FIG. 1. Multi-unit activity recorded from ulnar nerve at wrist upon release of cuff in upper arm following 20 min of ischæmia. B is direct continuation of A. *Upper trace*: mean voltage neurogram. *Second trace*: pulse plethysmogram from tip of fifth finger, marking re-establishment of circulation. *Third trace*: surface skin temperature at pulp of fourth finger. Vertical bar indicates magnitude of temperature shift. *Fourth trace*: EMG activity from hypothenar muscles. Vertical quadruplets mark trains of painful electrical stimuli to the skin within the ulnar territory in the hand.

As reflected by shifts in mean voltage neurogram, spontaneous activity started towards the end of the first minute after release of cuff: it peaked during the second minute, to decay over the ensuing 4 min. Prolonged paroxysmal bursts of impulses predominated during the most intense stage of discharge, when 'buzzing' and 'pseudocramp' prevailed. Towards the end of the second minute, rhythmically repeated bursts of shorter duration were recruited, and 'pricking' and 'tingling' dominated. Towards the end of the cycle in B, when the over-all activity was much decreased, bursts were even shorter though again spaced out; they repeated in complex rhythms. 'Tingling' was now the exclusive sensory correlate.

The '*pseudocramp*' started almost simultaneously with 'buzzing' and was often, but not necessarily, accompanied by moderate EMG activity and irregular muscle twitchings (fig. 1A): it was described as a vaguely localized, continuous sensation of tension deep in the hand, rather than in the skin, lasting until about the third minute. Activity in motor nerve fibres as expressed by EMG activity was surprisingly slight. It was confined to the period of most intense discharge in sensory fibres, and, on repetition of ischæmic periods, it dropped out before the paroxysmal discharges in cutaneous nerve fibres.

'*Pricking*' sensation followed about one and a half minutes after release; it was the most prominent sensation during the third minute, and slowly waned thereafter. 'Pricking' consisted of a 'feeling of rapidly repeated, irregularly-spaced, discrete, little pricks, less sharp and painful than the pin-pricks employed in the clinical testing of sensation; they are felt superficially in the skin' (Merrington and Nathan, 1949). During this period the over-all neural activity was often exaggerated by bursts with a marked tendency to repeat rhythmically (fig. 1A).

The last paræsthesiæ in the sequence consisted again of intermittent 'tingling'. It became apparent when the 'buzzing' sensation decreased, and there was often the feeling that high frequency 'buzzing' and low frequency 'tingling' were bridged by a continuum of intermediate frequencies. 'Tingling' persisted for between five to fifteen minutes and usually outlasted 'pricking'. 'Pricking' and 'tingling' could be recognized as separate qualities even while they co-existed. Both were extremely well localized to minute spots in the skin, but 'pricking' was very intense, almost painful, whereas 'tingling' was less intense, comparable to a flutter with marked rhythmicity. Whereas 'tingling' was mostly referred to the pulps of the fingertips, 'pricking' was referred more evenly to the palmar aspects of fingers and hand. During the period of 'tingling' the neural activity was dominated by brief rhythmically repeating bursts made of a few impulses; this activity could extend until the fifth to fifteenth minute (fig. 1B).

In general, there was a close correlation between the spontaneous post-ischæmic neural activity and the perception of paræsthesiæ, and it was usually possible to judge, by mere inspection of the neurogram, when paræthesiæ started, when they reached maximum and when they disappeared.

Paroxysmal Discharges in Single Units

The essential feature of the single unit discharges during the second and third minutes after release of the cuff, when the multi-unit activity and the paræsthesiæ were maximal, was the occurrence of relatively prolonged bursts of high frequency discharges. Examples of this kind of activity are shown in figs. 2 and 3. The bursts usually lasted for 1 to 7 seconds, successive bursts becoming progressively shorter. The impulse frequency within bursts reached a maximum of 200–280 Hz within the first 20 to 50 ms; it decreased exponentially thereafter. Firing frequency was regular, except at the very beginning and towards the end of the burst. Maximal impulse

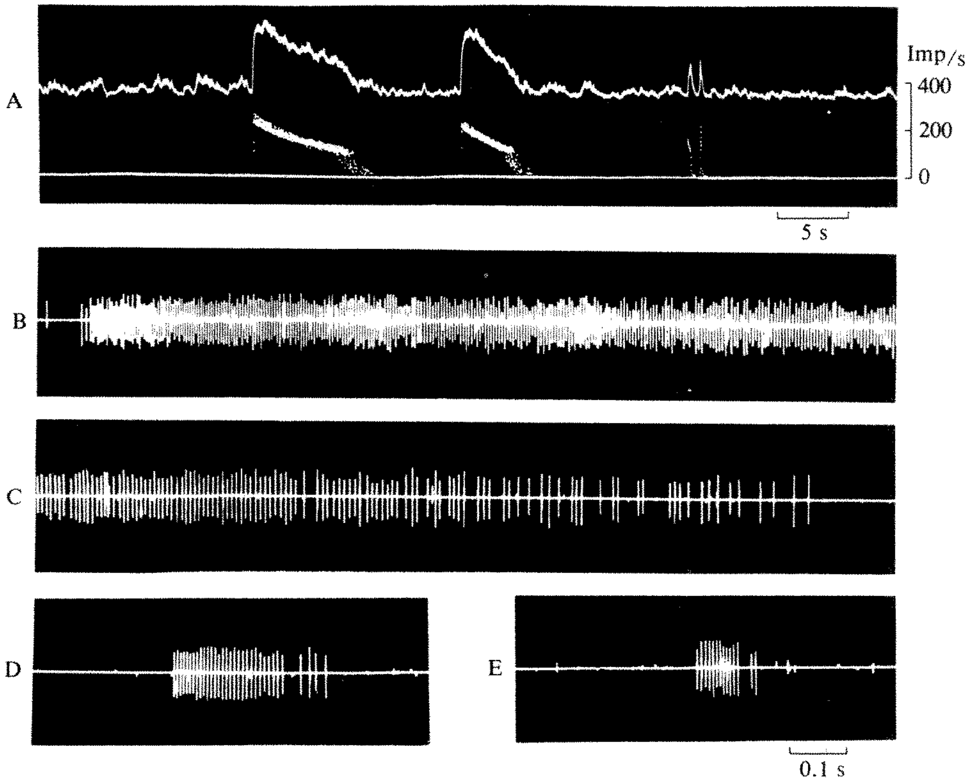

FIG. 2. Prolonged high-frequency discharges in a single unit recorded from the median nerve at elbow level. Unitary bursts appeared during the second minute after release of cuff compression round forearm, maintained for 25 min. A, integrated neurogram (*upper trace*) shows four abrupt deflections, representing single unit discharges, also displayed in B–E. 'Instantaneous' frequency plot (*lower trace*) shows initial frequency of about 220 Hz with exponential fall to about 150 Hz and subsequent break down. Duration of consecutive bursts diminished from an initial maximum of 7 s. B displays beginning and C the end of first unitary burst shown in A. Note regular firing frequency at the beginning, and missing beats towards the end. Last two bursts in A are displayed in D and E.

frequency became slightly lower in repeated bursts, and the decay of frequency was progressively steeper in successive bursts (fig. 3B). Such decay was uniform to a level in the region of 150–130 Hz when the frequency fell abruptly because of intermittent drop out of impulses (figs. 2 and 3B). Bursts repeated periodically at intervals of several seconds, sometimes quite regularly (fig. 3). Usually, a complete series of bursts covered under two minutes in time.

The single unit activity during the later stages of paræsthesiæ consisted of brief bursts that repeated rhythmically over prolonged periods of time (up to fifteen minutes). Examples of this kind of discharge are shown in figs. 4 and 5. This particular unit started discharging by the second minute after release, with occasional impulses that rapidly aggregated into periodic high frequency bursts (up to 330 Hz) with after-discharges of decaying mid-frequency firing lasting a second or more (fig. 4A). At this stage, the intervals between bursts were of the order of two or three seconds. After-discharges soon started to drop out (fig. 4B), and as the bursts became shorter so did the intervals between bursts (fig. 4C and D). Eventually, brief bursts of a few impulses repeated in gallop (fig. 5A), in triplets, twin or single regular discharges at short intervals between bursts of the order of tenths of a second (fig. 5B and C). Over the ensuing twelve minutes, the number of discharges per burst and the impulse frequency within bursts slowly decreased (fig. 5D and E).

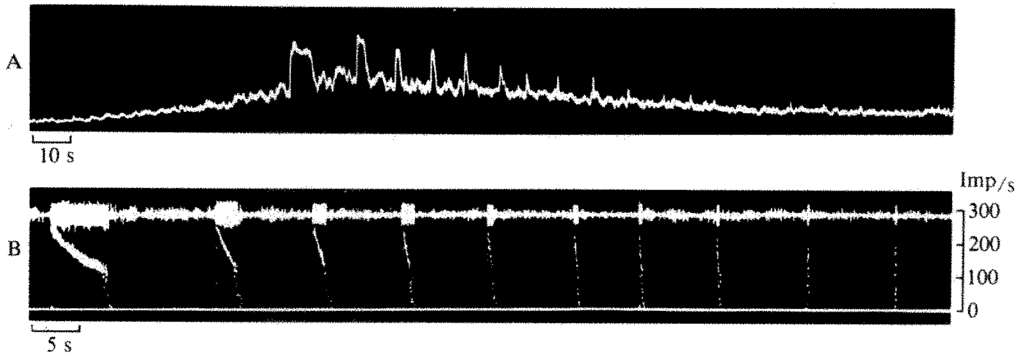

FIG. 3. Series of 10 high-frequency discharges from a single unit recorded from the ulnar nerve at elbow level during hyperventilation. A, integrated neurogram, dominated by single unit bursts. Recording started on release of cuff in upper arm after 15 min of ischæmia. B, part of the sequence shown in A, displayed at an extended time scale. *Upper trace* is original neurogram, *lower trace* displays 'instantaneous' firing frequency of the unit. Note the fairly regular repeat of bursts, and their decreasing duration. Note also the uniform impulse frequency at the onset of bursts and the progressive steepness of the frequency decay in subsequent bursts. As in fig. 2A, there seems to be a critical firing frequency of about 130 Hz, below which the impulse frequency decays abruptly.

Towards the end of the sequence of paræsthesiæ, when the only quality of perverse sensation reported was 'tingling', brief rhythmic discharges similar to those illustrated in fig. 5 were the only kind of spontaneous activity recorded from the nerve. It was often possible, by focusing attention on one point of referral to the skin, to discriminate definite rhythms of 'tingling' out of a chaotic interfering background. On one occasion, the subject, deprived of audiovisual feedback from the recording system, could report on the cessation of 'tingling' referred to a point in the pulp of the index finger within the receptive field of the impaled median nerve fascicle, at the same time as the unit stopped firing (fig. 5E).

Criteria applied to discriminate these patterns of discharge were based on duration of the bursts, and time and duration of their occurrence within the hyperexcitable cycle. These characteristics, however, may be circumstantial depending upon the level within the cycle of hyperexcitation at which the units were analysed. It is thus conceivable that these profiles of discharge might evolve into one another. Features common to them were:

(a) a striking aggregation of unit impulses into bursts;

(b) a tendency for bursts to repeat at more or less regular intervals, which were generally shortest during the mid-period of a bursting sequence;

(c) a very high maximal frequency of impulses (330–200 Hz) towards the onset of bursts;

(d) an exponential decay of impulse frequency and an increasing irregularity of impulse intervals within bursts down to a frequency of about 150–130 Hz, below which impulse generation became insecure;

(e) a progressive decrease in peak frequency, number of impulses per burst and burst duration with time.

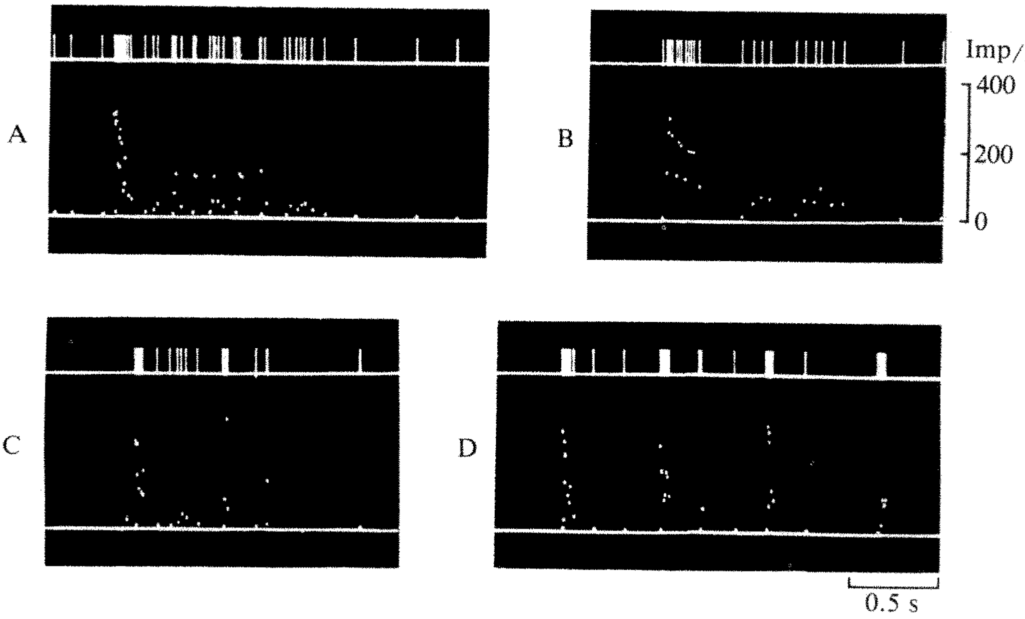

FIG. 4. Sequence of single unit impulses recorded from the median nerve at elbow level after ischæmia for 30 min with cuff in forearm. A is recorded 1 min 30 s, B, 1 min 35 s, C, 1 min 50 s and D, 3 min after release of the cuff. Note progressive development of a rhythm by the grouping of high-frequency discharges into short bursts, repeating at shorter intervals, and the progressive elimination of after-discharges.

Thus, a general rule behind spontaneous firing behaviour appeared to be a relatively rapid build-up of hyperexcitability in many nerve fibres followed by a slower decay. This is represented as characteristic shifts in the baseline of the integrated multifibre activity, as seen in figs. 1, 3A, 7, 8A. Despite a sustained state of general hyperexcitability, the discharges at the single unit level were discontinuous; they occurred in bursts, suggesting cyclical excitation and depression in the individual nerve fibres. No obvious signs of interaction between hyperexcitable fibres were observed.

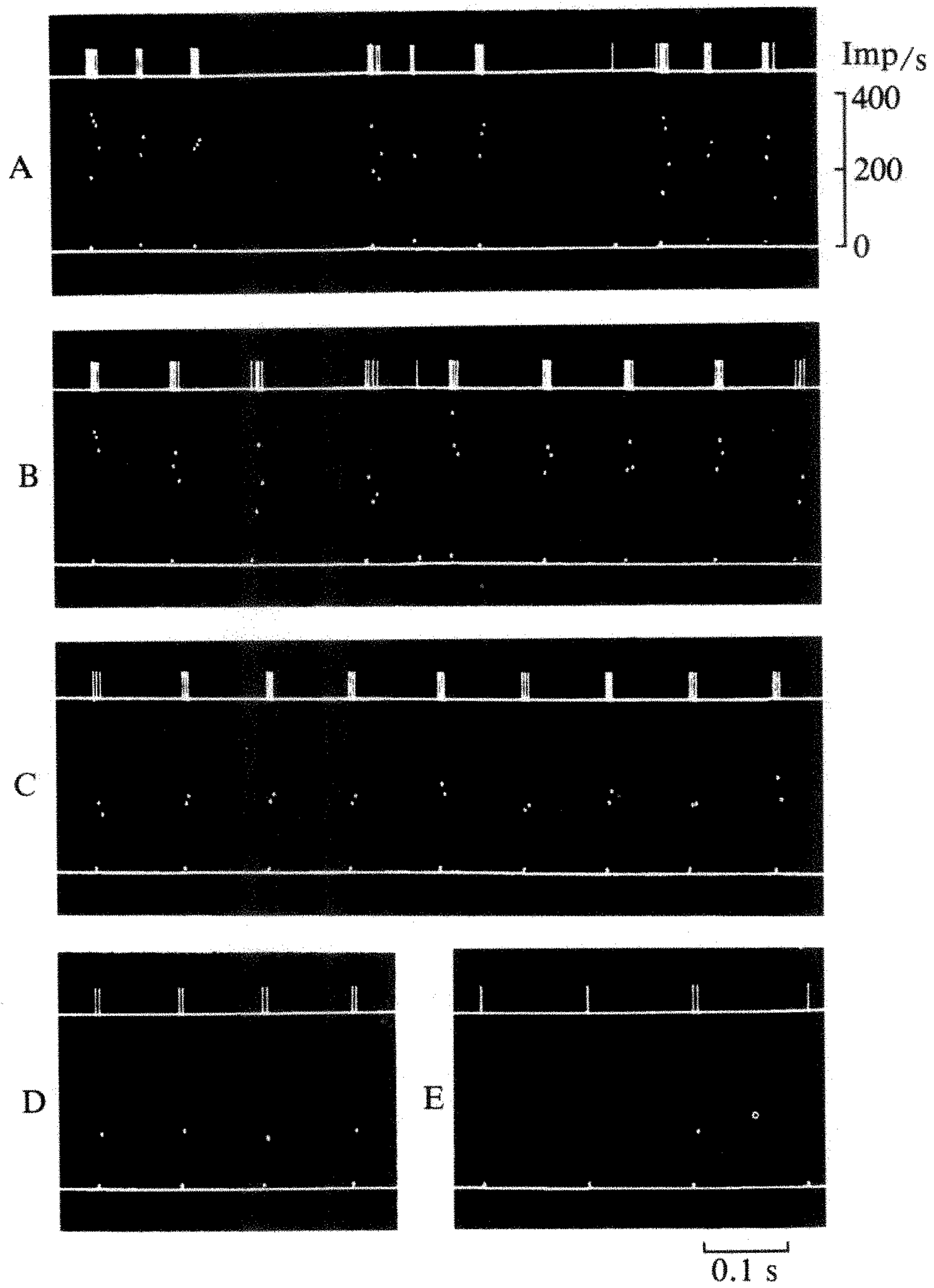

FIG. 5. Same unit as shown in fig. 4. Samples A–E cover a sequence from the sixth to fourteenth minute after ischæmia. Gallop rhythm in A evolved into a monotonous rhythm (B–E), together with a progressive reduction in number of spikes per burst. Unit ceased to fire at E, when subject reported cessation of rhythmic 'tingling' referred to index finger-tip. Note different time scales for figs. 5 and 4.

Cumulative Effects of Compression-ischæmia

The repetition of experiments, at short intervals of 5 to 10 minutes, progressively exhausted paræsthesiæ. Fig. 6 shows paroxysmal neural activity in the ulnar nerve during the first post-ischæmic period (A), and a complete abolition of paroxysmal discharges in the sixth post-ischæmic period, using the same recording site (B). In the absence of paroxysmal neural activity no paræsthesiæ were felt.

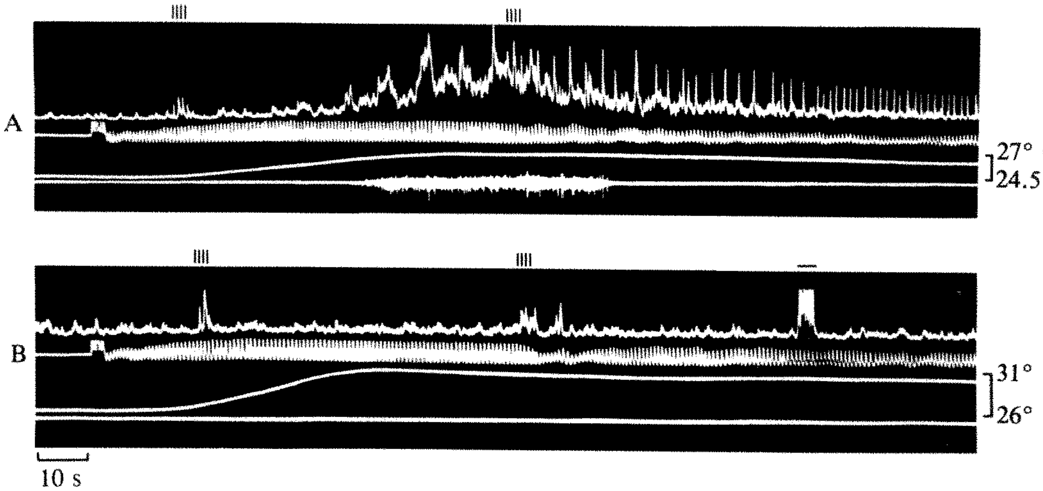

FIG. 6. Exhaustion of paroxysmal activity despite normal conduction in myelinated and unmyelinated fibres in repeated post-ischæmic periods. A is identical with fig. 1A and illustrates intense spontaneous activity in the first post-ischæmic period in a series. B, identical recording site as A, during the sixth post-ischæmic period. Paroxysmal discharges and paræsthesiæ were abolished, but the initial warm-hot sensation on release of ischæmia still occurred as usual. Horizontal bar marks responses in large mechanoreceptive afferents to touch stimuli applied to cutaneous receptive field. Irregular fluctuations in the neurogram represent normal sympathetic outflow to the skin. Vertical quadruplets in A and B mark trains of painful electrical stimuli to the skin, inducing prominent sympathetic reflex responses (Hagbarth *et al.*, 1972). Vasoconstriction from reflex activation of sympathetic vasomotor fibres is expressed in the pulse plethysmogram (*second trace, centre*), except during apparent vasoparalysis early after re-establishing circulation.

Effects of Hyperventilation

Hyperventilation consistently enhanced both post-ischæmic discharges and paræsthesiæ. This is illustrated in fig. 7. In this case, the anticipated decrement in over-all neural activity following repetition of ischæmia did not occur during hyperventilation. On the contrary, activity increased and was extended in time in comparison with previous control. In addition, multiple high frequency bursts in individual units dominated the recording, indicating recruitment of previously silent units into paroxysmal discharges.

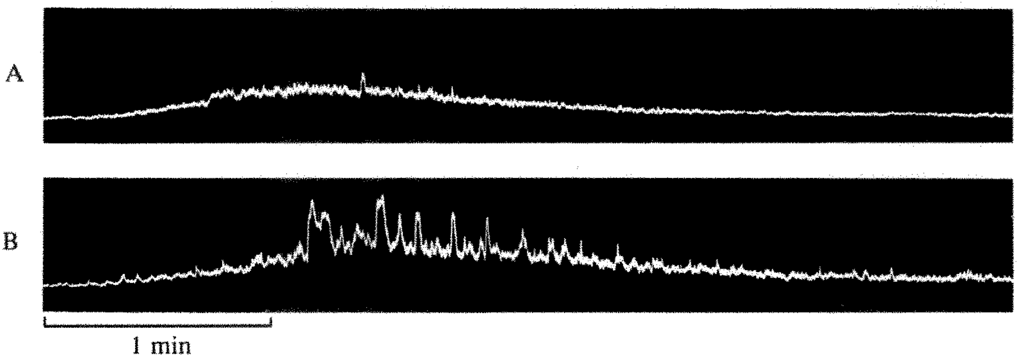

FIG. 7. Effect of hyperventilation on post-ischæmic discharges. Mean voltage neurograms in A and B obtained from the same intrafascicular recording site in ulnar nerve at elbow level following repeated ischæmic periods for 15 min induced by cuff in upper arm. Records start on release of cuff. A, second run, showing moderate post-ischæmic activity. B, third run, 10 min after A. Marked increase in paroxysmal activity and more pronounced paræsthesiæ as compared with A.

Local Anæsthetic Blocks

A few experiments were performed during local nerve blocks to explore the question of the site of origin of paroxysmal discharges. Recordings were obtained at wrist level from a median nerve fascicle innervating a small skin area in the tip of the index finger. A lidocaine block of both digital nerves was performed at the base of the index finger. It was found that 'buzzing', 'pricking' and 'tingling', referred to the index finger, and the corresponding neural discharges continued to occur after nerve block, albeit somewhat decreased as compared to pre-anæsthetic control (fig. 8).

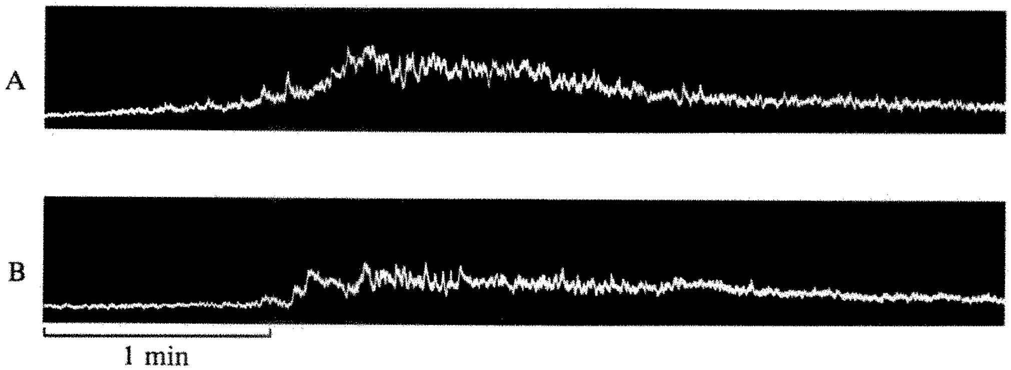

FIG. 8. Persistence of post-ischæmic discharges despite local anæsthetic block of terminal nerve segments. Mean voltage neurograms in A and B obtained from the same intrafascicular recording site in the median nerve at wrist level. Receptive field in index finger. A, post-ischæmic neural activity recorded on release of cuff in upper arm. B, second run 40 min later. Index finger anæsthetized by lidocaine. Paroxysmal neural discharges were not abolished. Note lack of typical increase in neural activity during the first minute after release. Correspondingly, early post-ischæmic warm-hot sensation was not perceived in index finger.

This means that the impulses recorded (and perceived) must have originated in the nerve fibres, proximal to the site of the block, and not primarily in peripheral receptors.

In a separate experiment, recordings were obtained at wrist level from an ulnar nerve fascicle innervating the little finger, and the ulnar nerve was blocked with lidocaine at elbow level, 4 cm distal to the cuff. During the post-ischæmic period, the subject could perceive paræsthesiæ referred to median, but not to ulnar nerve distribution. Nevertheless, striking spontaneous rhythmic activity was recorded from ulnar sensory nerve fibres (fig. 9). The experiment provides evidence that paroxysmal discharges of the type which typically underlie paræsthesiæ can be generated along the uncompressed nerve fibres distal to the cuff.

Types of Fibres Engaged in Paroxysmal Activity

During the post-ischæmic period, repetitive responses to single brief electrical stimuli (0.1 ms at 1.5 × threshold) to the skin were observed in two units. The calculated conduction velocities in the peripheral segments of these fibres were 45 m/s and 42 m/s. This indicates that myelinated fibres had become hyperexcitable.

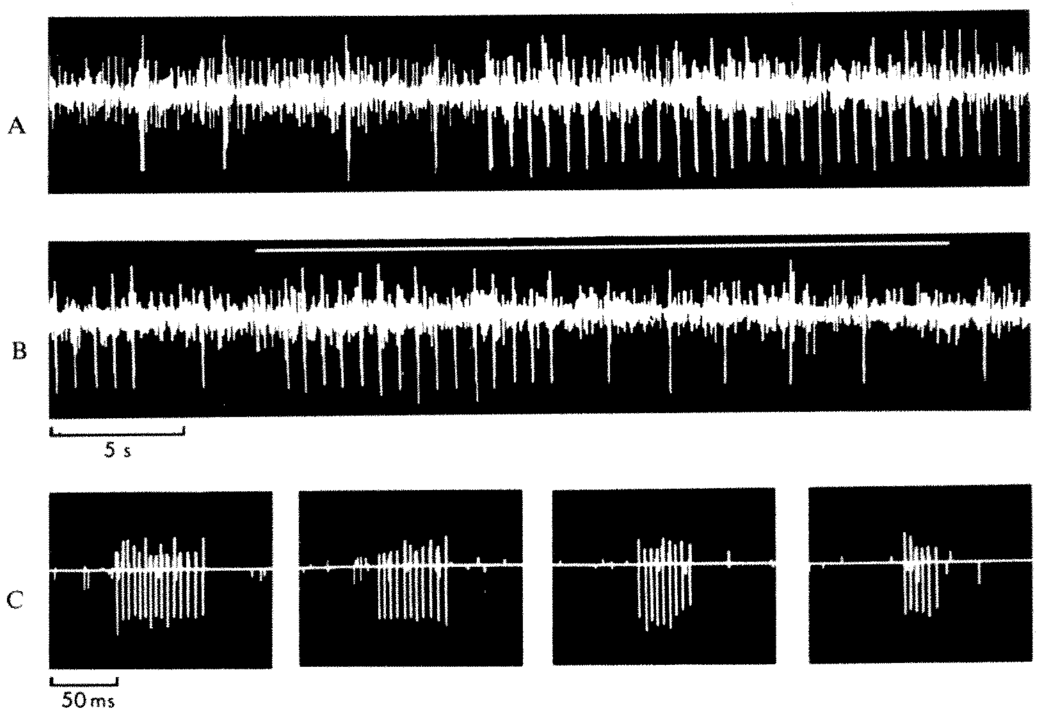

FIG. 9. Spontaneous activity generated in ulnar nerve fibres distal to the site of cuff compression. A, upon release of cuff in upper arm, bursting discharges were recorded at wrist level. Anæsthetic block of ulnar nerve at elbow prevented impulses from reaching conscious levels, and from propagating antidromically from the site of compression. B, temporary revival of rhythmically repeated bursts during hyperventilation (white bar). C, sequence of unitary bursts extracted from A, displayed at an expanded time scale.

Receptor characteristics of hyperexcitable sensory units were not identified, but the observation that the post-ischæmic paræsthesiæ included vibratory or tactile sensations, referred predominantly to glabrous skin of the fingers and the palm of the hand, and could be exaggerated by gentle tapping on the skin, suggests that large myelinated fibres with low threshold mechanoreceptors participated in the paroxysmal discharge.

There was no indication that small calibre fibres were rendered hyperexcitable. Indeed, there were no obvious signs of sympathetic overaction, although a normal increase of skin-sympathetic activity might occur during arousal by paræsthesiæ. Further, there was no spontaneous sensation of cold post-ischæmically. Paræsthesiæ were not painful, although ischæmic muscle pain would complicate the picture following voluntary muscle contraction, prior to release. The above could not be explained by ischæmic block of unmyelinated fibres, since sensations of pain and warmth could be evoked and sympathetic reflex responses could be elicited shortly after re-establishment of circulation (fig. 6).

As described previously by Nathan (1958), pain perception was considerably blunted during the height of post-ischæmic paræsthesiæ. In order to maintain a certain subjective intensity level of pain in the experiment shown in fig. 6, the stimulus intensity of electrical shocks to the skin had to be raised by about 50 per cent during the height of paræsthesiæ(fig. 6A) relative to controls before paræsthesiæ and when paræsthesiæ were exhausted (fig. 6B).

Warm and Hot Sensations

A few seconds after the warm arterial blood blushed the cold cyanotic limb there was a sensation of increasing warmth and non-painful heat, lasting for about a minute. This sensation approximately paralleled the phase of increase in pulse amplitude (fig. 6), although the measured increase in skin temperature of the fingertip lagged behind. The warm-hot sensation had a normal quality, but it was clearly excessive relative to the control hand. Repetition of ischæmia, which exhausted 'buzzing', 'pseudocramp', 'pricking' and 'tingling' did not change the warm-hot sensation, which was characteristically present at the early stage of repeated post-ischæmic periods (fig. 6). After local anæsthetic block of the index finger as described in fig. 8B, the typical early increase in neural activity during the first minute (figs. 3A, 7, 8A) was less prominent, and there was no sensation of warmth in the index finger. Such observations suggest that the early increase in neural activity was, at least in part, due to afferent impulses from warm receptors, and that the warm-hot sensation did not arise from ectopic impulses generated along unmyelinated nerve axons.

DISCUSSION

Adrian's dream 'to compare both stimulus and sensation with the messages which pass up the sensory nerve fibres . . . ' (Adrian, 1931), materialized when Hensel and Boman (1960) recorded single sensory nerve fibre activity from surgically exposed nerves in alert subjects; it became scientific routine when percutaneous 'microneurography' was introduced (Vallbo and Hagbarth, 1968). The present study inaugurates the microneurographic technique in the field of abnormal sensation, specifically in the area of positive phenomena. The results largely confirm the predictions (Lewis *et al.*, 1931; Zotterman, 1933; Kugelberg, 1944; Weddell and Sinclair, 1947; Gordon, 1948; Merrington and Nathan, 1949; Gilliatt and Wilson, 1953) that paræsthesiæ from nerve dysfunction involve spontaneous afferent activity.

This study adds objective verification to the knowledge advanced in previous clinical inquiries on the topic. The comprehensive clinical study by Merrington and Nathan (1949) using themselves, together with W. R. Trotter and patients with strategic neurological lesions as subjects, yielded convincing data on the nature, source, nerve fibre type responsible, and central pathways for post-ischæmic paræsthesiæ. Of the many issues which emerge from our results, the following seem most pertinent.

Spontaneous Versus Injury Discharges

That normal nerve fibres within an abnormal milieu may reversibly behave as ectopic generators of impulses has been documented in motor units in man (Kugelberg, 1944; Kugelberg and Cobb, 1951) and is substantiated here for human sensory fibres too. However, it might be argued that the discharges reported here are simply due to injury inflicted by the intraneural recording electrode. Indeed, the various injury discharges that follow nerve section (Adrian, 1930) are remarkably similar to the post-ischæmic sensory discharges reported here. Adrian described three types of injury discharges in individual fibres: '(1) A continuous and regular succession of impulses at a high frequency which changes very gradually and is rarely less than 150 a second' (compare with fig. 2B). '(2) An irregular succession at a lower frequency (below 150 a second)' (compare with fig. 2C). '(3) A grouped discharge; each group consisting of several impulses very closely spaced and the successive groups following one another at... 10 a second or less' (compare with fig. 5). In spite of this resemblance, it is most unlikely that the discharges we have recorded in man during paræsthesiæ were caused by needle injury, since they correlated consistently in time with characteristic paræsthesiæ, which in turn followed consistently after release of compression-ischæmia, regardless of whether or not the nerve had been impaled for recording. Thus, we conclude that nerve fibres in the hyperexcitable stage have a limited repertoire of reactions to stimuli of quite different nature.

Site of Origin of Paroxysmal Discharges

A priori, the abnormal discharges might be anticipated to originate under the site of the compressing cuff, along the ischæmic nerve or from the sensory end organs. Among the earlier studies that attempted to explore this question, Gordon's (1948) and Merrington and Nathan's (1949) are notable for their indirect demonstration that the impulses responsible for post-ischæmic paræsthesiæ are generated in nerve fibres and not primarily in end-organs as proposed by Weddell and Sinclair (1947), and that they arise from throughout the length of the nerve fibre subjected to ischæmia rather than from just under the area compressed by the cuff, as proposed by Lewis *et al.* (1931) and by Zotterman (1933). Our own experiments using local anæsthetic blocks endorse the concept that the discharges underlying paræsthesiæ originate along nerve fibres previously subjected to ischæmia.

Types of Nerve Fibres Recruited into Paroxysmal Discharges

Early judgements passed on the type of sensory fibres presumed to discharge spontaneously during post-ischæmic paræsthesiæ were unavoidably based on speculation. Lewis *et al.* (1931) incriminated 'touch fibres' for 'tingling', whereas Zotterman (1933), Kugelberg (1944) and Weddell and Sinclair (1947) heavily incriminated 'pain fibres'. Lewis *et al.* (1931) were preoccupied with the 'pseudocramp' and related it to activity in muscle afferents. Merrington and Nathan (1949) put together bits of clinical evidence that allowed them to make a case for fibres mediating touch, pressure and position sense being the respective sources and the conductors of 'buzzing or tingling', 'pricking' and 'pseudocramp'. With the same clarity as they had dismissed end-organ origin, they excluded pain and sympathetic fibre participation.

Using surface electrode recordings from the median nerve, Seneviratne and Peiris (1968) observed signs of hyperexcitability in large sensory fibres as indicated by increased amplitude of the response to submaximal electrical stimulation during the post-ischæmic period. This has been confirmed and studied further by Stöhr, Gilliatt and Willison (1980), who found that the striking abnormality in this phase was the increased excitability of large sensory fibres to a second shock delivered 3 to 20 ms after the first, that is, during the supernormal period. Similar changes in human motor fibres have been described by Bergmans (1970).

Our results further endorse the concept that myelinated fibres become hyperexcitable and contribute paroxysmal discharges. For example, we observed repetitive responses to brief electrical shocks during paræsthesiæ in fibres with conduction velocities in the large myelinated range; and the high firing frequencies in the unitary bursts, up to 330 Hz is consistent with activation during the supernormal period in large fibres. In a patient with neuromyotonia, actual identification of spontaneously discharging units with slowly adapting (SA) and rapidly adapting (RA) mechanoreceptors was achieved during ischæmia in parallel with the development of paræsthesiæ (Lance, Burke and Pollard, 1979).

Unmyelinated C units in man normally have a limited capacity to discharge at high frequencies (Torebjörk and Hallin, 1974), but it remains unknown whether under the present abnormal circumstances they might become hyperexcitable and increase their firing rates to the levels observed here. It is interesting, however, that during ischæmia from arterial ligation in rabbits, Lynn (1979) observed no change in background firing of previously sensitized nociceptor units with C fibre axons. It is consistent with this that there was no report of pain in normal subjects, during or following compression ischæmia in a resting extremity. On the contrary, the perception of painful stimuli was considerably depressed in the area to which intense paræsthesiæ were referred during the post-ischæmic period, presumably because of central inhibition of the nociceptive input by the enormous afferent barrage in large myelinated fibres (Zotterman, 1933; Nathan, 1958; Melzack and Wall, 1965). The possibility that the absence of spontaneous painful paræsthesiæ might simply be due to ischæmic block of the pertinent fibres was ruled out by the observations that (a) pain is hardly blocked after thirty minutes of ischæmia and (b) that perception of painful stimuli returned to normal after the occurrence of paræsthesiæ had been exhausted in repetitive experiments (fig. 6).

The striking warm-hot sensation following release of the cuff is not thought to be due to ectopic impulses generated along unmyelinated nerve axons, but rather due to activation of warm receptors (Ebbecke, 1917; Bazett and McGlone, 1932; Merrington and Nathan, 1949). We have confirmed this observation. The disproportion in intensity of the warm-hot sensation relative to the basal state may result at least in part from an overshoot in the response of dynamic warm receptors to a sudden increase in temperature (Konietzny and Hensel, 1977), and it is possible that metabolic factors may also enhance the receptor responses (Bazett and McGlone, 1932).

Thus, we conclude that unmyelinated fibres neither block nor engage in ectopic impulse generation under the present circumstances.

Correlations Between Neural Activity and Types of Paræsthesiæ

The fundamental question of what determines the types of paræsthesiæ cannot be answered directly. Indeed, one would like to correlate discharges in defined types of hyperexcitable sensory units with types of paræsthesiæ, but the identity of spontaneously discharging units has not been established. Alternatively, a correlation between the discharge characteristics in multi- and single-fibre recordings and types of paræsthesiæ has been sought.

There was in fact a gross correlation in time between the prolonged high frequency discharges and sensations of continuous 'buzzing' and 'pseudocramp', and between shorter rhythmically repeated bursts and intermittent 'pricking' and 'tingling' during the later stages of the post-ischæmic period (fig. 1). Those relationships could be sharpened further and allow tentative dismissal of 'pseudocramp' from the picture. The signals described were recorded from sensory fascicles and there is evidence pointing toward 'pseudocramp' being proprioceptive and hence subserved in motor fascicles. Merrington and Nathan (1949) largely elucidated the source and pathways conducting 'pseudocramp': fibres subserving 'sense of movement and position' in nerves and posterior columns were strongly implicated. Recent discrimination of the various proprioceptive functions permits one to identify the 'pseudocramp' with the sense of tension or dynamæsthesia (Roland, 1973), and therefore to attribute it to impulses in afferents from Golgi tendon organs (Matthews, 1977; Roland and Ladegaard-Pedersen, 1977). 'Buzzing' therefore emerges as a likely sensory correlate of activity in appropriate exteroceptive units which fire with prolonged high frequency discharges.

That brief rhythmic discharges are a probable correlate of intermittent 'tingling' towards the end of post-ischæmic paræsthesiæ is supported by the observation that such discharges and 'tingling' coexisted for several minutes when all other types of paræsthesiæ had vanished. In an isolated experiment, rhythmical discharges which had become simplified to paired or even single impulses (fig. 5 D, E) correlated in time with the sensation of faint rhythmical tingling referred to a discrete point within the appropriate receptive field in the index finger-tip. It was striking that the sensation of tingling stopped when the unit ceased firing. This might be mere coincidence; however, Vallbo and Johansson (1976) have demonstrated that even single impulses from RA units from the finger-tip may reach consciousness.

As to 'pricking', its intermittent character and its occurrence in time during the hyperexcitable cycle suggest that brief bursts of impulses in appropriate sensory units might be the underlying neural event.

We do not believe that the whole spectrum of paræsthesiæ results from modulation of the pattern of discharge only in a particular type of sensory unit. On the contrary, the distinctly different qualities of paræsthesiæ indicate that different types of sensory units are specifically engaged. For instance, the tactile quality of 'tingling' and its preferential referral to minute points in the finger tips suggest an afferent input from mechanoreceptive units for fine tactile discrimination, with small receptive fields, such as RA and slowly adapting type 1 (SA1). (Johansson and Vallbo, 1979). Such units populate mainly the finger-tips (Johansson and Vallbo, 1976). 'Tingling' was described as a low-frequency flutter, and 'buzzing' had the character of high-frequency vibration. It is conceivable that discharges in RA and Paccinian corpuscle (PC) units contribute to these paræsthesiæ, since such units are thought to signal flutter and vibration (Talbot, Darian-Smith, Kornhuber and Mountcastle, 1968). 'Pricking' was also referred to minute spots in the hand, but was distinctly different in character from 'tingling and buzzing', being very sharp, almost painful. 'Pricking' perhaps results from discharges in A delta fibres belonging to a discriminative nociceptive system, the painful component of the percept being attenuated by the ongoing activity in large mechanoreceptive afferents. It must be emphasized, however, that the tentative association of activity, in particular sensory unit populations with various types of post-ischæmic paræsthesiæ, is based on a number of assumptions. Work is now in progress to test the validity of such assumptions.

Paræsthesiæ are often referred to as 'perverted sensations', although the character of the sensory distortion is seldom defined. Obviously paræsthesiæ are abnormal in the sense that they result from ectopic impulse generation in nerve fibres as distinct from the natural activation of receptors. Furthermore, as seen in our recordings, the impulse frequency in hyperexcitable fibres may be very high, near maximal impulse frequency for various mechanoreceptors in the skin of the hand (Knibestöl and Vallbo, 1970), and individual units may fire in paroxysmal bursts independent of activity in other fibres. The maximal activation of an individual mechanoreceptor in the skin without concomitant excitation of adjacent receptors with overlapping receptive fields is highly abnormal, since 'practically all naturally occurring tactile stimuli to the human hand excite a large number of sensory units, setting up a pattern of neural activity from the population of mechanosensitive units' (Johansson and Vallbo, 1976). The normal spatio-temporal pattern of impulses in populations of sensory units is upset during paræsthesiæ, and replaced by high-frequency bursting discharges, appearing asynchronously in multiple sensory units of different types and with different central connections. This would create a chaotic percept consisting of an assortment of sensations referred in irregular succession to multiple areas. This is the essential feature of paræsthesiæ.

SUMMARY

Intraneural microelectrode recordings were obtained from sensory nerve fascicles in awake normal subjects experiencing post-ischæmic paræsthesiæ. Spontaneous activity in afferent fibres started about half a minute after re-establishment of circulation; it peaked by the second minute and slowly waned thereafter. This parallelled the time course and intensity of the perceived paræsthesiæ. During the most intense stage of paræsthesiæ, single unit discharges consisted of prolonged bursts of high-frequency impulses (200–300 imp/s) lasting for 1 to 7 seconds. Repeated bursts became progressively shorter and often exhibited marked rhythmicity as paræsthesiæ became weaker. Hyperventilation increased paroxysmal firing and paræsthesiæ, whereas ischæmic periods repeated at short intervals exhausted the impulse generating mechanism. The outcome of local anæsthetic blocks indicated that the impulses were generated ectopically along the nerve fibres previously subjected to ischæmia and not primarily from the receptors in the skin. The high frequency of the discharge and the quality and distribution of various paræsthesiæ suggest that sensory units with myelinated fibres participated in the paroxysmal discharge; normal activity, but no ectopic discharges were recorded in unmyelinated fibres. It is proposed that the perverted quality of paræsthesiæ is due to an abnormal spatio-temporal pattern of ectopic impulses from different types of sensory units, creating a chaotic percept consisting of an assortment of sensations referred in irregular succession to multiple areas.

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THE CLINICAL COURSE OF SUBDURAL HÆMATOMA

A RETROSPECTIVE STUDY OF ÆTIOLOGICAL, CHRONOLOGICAL AND PATHOLOGICAL FEATURES IN 212 PATIENTS AND A PROPOSED CLASSIFICATION

by A. R. WINTZEN

(*From the Department of Neurology, University Hospital, Leyden, The Netherlands*)

INTRODUCTION

THE variable clinical course of subdural hæmatoma has until now frustrated all attempts to categorize the various forms unequivocally.

One method of classifying subdural hæmatoma is according to the ætiology of the disorder. The subdivisions used are 'spontaneous' and 'traumatic' and although attractively simple at first sight they lead to substantial difficulties in practice. The term 'spontaneous' is incompatible with current philosophy that disorders must have a cause, whether or not this cause be known. 'Trauma', according to *The Shorter Oxford English Dictionary* (1972) is a 'morbid condition of body produced by wound or external violence'. Many cases of subdural hæmatoma have not experienced trauma defined in this way, but are often assumed to be preceded by 'slight trauma', for example, coughing. Such reasoning may justifiably be considered gratuitous.

A frequently used classification is the chronological classification, which subdivides subdural hæmatoma into acute, subacute and chronic forms. The boundaries between these subdivisions are, however, quite arbitrary. Moreover, as the disorder often takes a biphasic course consisting first of an asymptomatic followed by a symptomatic phase, one should specify to which one of these two phases the terms apply. The asymptomatic phase may last for some considerable time and so deserve the eponym 'chronic', whereas the symptomatic phase in the same patient may be explosive, thus justifying the description 'acute'. This will be illustrated later.

The underlying pathology of the meninges is an important index of the age of the subdural hæmatoma (Munro and Houston Merritt, 1936), but unfortunately, few publications or records include a full description of meningeal status. Several authors (Munro, 1942; Logue, 1951; McKissock, Richardson and Bloom, 1960) have reported that associated brain injury, that is contusion or laceration, worsens the prognosis. Accordingly this is an important factor to be considered in a classification.

The aim of the present study is, therefore, to investigate the possibility of rubrication of subdural hæmatoma on the basis of the following criteria:

(1) ætiology of the subdural hæmatoma with respect to the presence or absence of trauma;
(2) chronology of the subdural hæmatoma, considering the durations of the asymptomatic and symptomatic phases;
(3) associated cerebral pathology, particularly contusion and laceration;
(4) outcome in terms of survival and the quality of survival.

PATIENTS AND METHODS

Files from the Departments of Neurology and Neurosurgery covering the period 1959 to 1978 (inclusive) were reviewed and yielded 212 cases finally diagnosed as subdural hæmatoma.

The diagnosis was established by operation in 205 cases, by autopsy in 5 and by computerized tomography (CT) in 2 cases. A number of details were considered in all files and these are listed below:

(1) presence or absence of trauma. Trauma was only considered to be present when it fitted the definition quoted above, irrespective of whether the injury seemed to involve the body only or also the head, a point often unclear in the case notes. Cases were, therefore, considered to be traumatic when there was a history of mechanical force, clearly in excess of everyday events, acting upon the body or the head, irrespective of whether this was remembered by the patient or his family on admission or at a later stage;

(2) time which had elapsed between trauma (if present) and first manifestations: asymptomatic phase. Even if symptoms of cerebral concussion were present initially, provided they disappeared within hours or a few days, this phase was still considered to be asymptomatic;

(3) time which had elapsed between first manifestations and admission to hospital on account of symptoms. The time of admission was chosen because it is an easily established marker in all patients' histories, and because it is likely that at this time, the disorder had reached a degree of severity sufficient to warrant admission. This particular point in time was, of course, also determined by the diagnostic skill of the attending physicians. One hopes, however, that the latter factor did not have a great influence on the features of the series, as so many physicians were involved;

(4) associated cerebral pathology. This includes presence of cerebral contusion, laceration or hæmatoma, usually established during operation in most patients but at autopsy in some cases. In this series no consistent data on the age of the membranes of the hæmatomas were available.

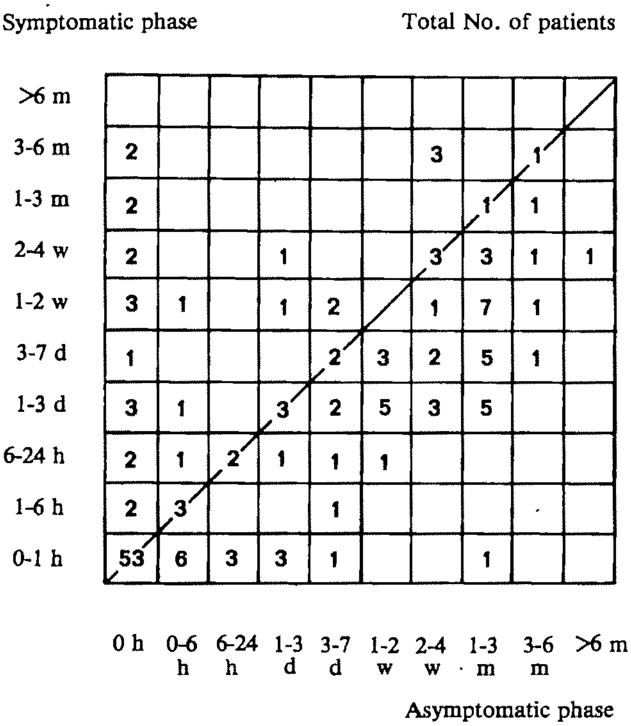
(5) etiological factors other than trauma. Under this heading, factors such as epilepsy, abuse of alcohol, vascular malformation, hæmorrhagic diathesis, anticoagulant therapy, lumbar puncture, ventriculo-atrial drainage, craniotomy and hypertension were considered.

(6) outcome. The outcome was categorized into death or survival, and complete or incomplete recovery as assessed upon discharge. A patient was considered to have recovered completely when he had no complaints and when there were no abnormal neurological signs on routine neurological examination. A detailed study of mental functions was not carried out routinely. Minimal neurological signs which did not hinder the patient were ignored.

RESULTS

A. *Cases in Whom Trauma was Present*

Chronology. There were 154 cases in whom trauma was present and in whom the duration of both asymptomatic and symptomatic phases could be established from the case notes. The first question investigated was whether the respective durations of the initial asymptomatic and subsequent symptomatic phases are related. Consequently they were plotted against each other, as shown in fig. 1.



Symptomatic phase	0 h	0-6 h	6-24 h	1-3 d	3-7 d	1-2 w	2-4 w	1-3 m	3-6 m	>6 m
>6 m										
3-6 m	2						3		1	
1-3 m	2							1	1	
2-4 w	2			1			3	3	1	1
1-2 w	3	1		1	2		1	7	1	
3-7 d	1				2	3	2	5	1	
1-3 d	3	1		3	2	5	3	5		
6-24 h	2	1	2	1	1	1				
1-6 h	2	3			1					
0-1 h	53	6	3	3	1			1		

FIG. 1. Distribution of cases according to duration of asymptomatic and symptomatic phases.

It is clear from this figure that not every combination of durations has an equal probability. A large number (53) of patients is found near the origin. These patients did not show an asymptomatic phase and were admitted immediately, that is, within one hour after trauma, and might therefore be designated as 'emergency' (E) cases. The ordinate represents a different group of patients, who showed neurological signs immediately after trauma. Although these signs persisted, the patients were not admitted straight away, and in some cases six months elapsed before admission. Apparently the symptoms were not properly interpreted during this period. The abscissa represents a group of 14 patients, in whom an asymptomatic phase with duration varying from several hours to months, was followed by suddenly developing symptoms, leading to immediate hospital admission.

Most of the remaining cases lie close to and below the diagonal. In these, the symptomatic phase tends to be slightly shorter than the asymptomatic phase. In only one case did the asymptomatic phase last for more than six months, and the symptomatic never exceeded six months, indicating that a protracted course of such magnitude is extremely unlikely to occur.

The figure shows decisively that there is no chronological basis for a clear-cut distinction between acute, subacute and chronic subdural hæmatoma. The cases form a complete spectrum of clinical course varying widely in terms of time.

Symptomatic phase

	0 h	0-6 h	6-24 h	1-3 d	3-7 d	1-2 w	2-4 w	1-3 m	3-6 m	>6 m
>6 m										
3-6 m										
1-3 m										
2-4 w	1			1					1	
1-2 w	1						1			
3-7 d					2			1		
1-3 d	1			2	1			1		
6-24 h	2		1		1					
1-6 h		2								
0-1 h	40	5	3	1				1		

Asymptomatic phase

FIG. 2. Number of patients with fatal outcome. Mortality rate and time intervals. Note high death-rate of emergency (E) cases in left bottom corner.

Outcome. In fig. 2, outcome is related to time-course. Obviously, the more rapidly evolving cases are associated with a higher mortality, which reaches its maximum in E cases. On the other hand, the mortality rate in this series is zero if the symptomatic phase exceeds four weeks. Full recovery is, however, possible with any time-course (fig. 3) and is common in cases with both longer asymptomatic and symptomatic phases, but extremely rare in E cases: only 2 of 53 patients recovered completely. Incomplete recovery is the most probable outcome in surviving E cases and is not exceptional in any other type (fig. 4).

Symptomatic phase

	0 h	0-6 h	6-24 h	1-3 d	3-7 d	1-2 w	2-4 w	1-3 m	3-6 m	>6 m
>6 m										
3-6 m	2						3			
1-3 m	2								1	
2-4 w	1						2	2		1
1-2 w	1	1			2			5	1	
3-7 d						2	2	3	1	
1-3 d	1			1	1	5	2	3		
6-24 h		1	1			1				
1-6 h	2				1					
0-1 h	2	1		1	1					

Asymptomatic phase

FIG. 3. Number of patients who recovered completely. Full recovery and chronological parameters. Note poor outlook for E cases in comparison with Figs. 1 and 2.

Symptomatic phase

	0 h	0-6 h	6-24 h	1-3 d	3-7 d	1-2 w	2-4 w	1-3 m	3-6 m	>6 m
>6 m										
3-6 m									1	
1-3 m								1		
2-4 w							1	1		
1-2 w	1			1				2		
3-7 d	1					1		1		
1-3 d	1	1					1	1		
6-24 h				1						
1-6 h		1								
0-1 h	11			1						

Asymptomatic phase

FIG. 4. Number of patients who recovered incompletely. Survival with residual deficit and chronological parameters. Note wide scatter of cases with phases of longer duration.

Therefore, although a definite trend exists, one cannot find an absolute basis for classification according to combined chronological and prognostic features. Again there is a complete range of possible outcomes for each time interval.

Symptomatic phase

	0 h	0-6 h	6-24 h	1-3 d	3-7 d	1-2 w	2-4 w	1-3 m	3-6 m	>6 m
>6 m										
3-6 m										
1-3 m										
2-4 w										
1-2 w	2									
3-7 d										
1-3 d	2	1			1	2	1			
6-24 h	2	2	1	1	1					
1-6 h										
0-1 h	43	4	2	1						

Asymptomatic phase

FIG. 5. Number of patients with associated brain contusion. Brain injury and time intervals. Note high incidence in E cases and scatter of cases with longer duration of phases.

Brain injury. The present series confirms the commonly encountered association of brain injury in E cases (fig. 5). Brain injury is, however, by no means restricted to the E group: it was encountered in cases with an asymptomatic phase of up to four weeks and a symptomatic phase of up to two weeks. Again the combination of chronological with pathological criteria does not provide a successful basis for classification. An interesting, though not surprising, point is the high correlation between mortality rate and brain injury, revealed from a comparison of figs. 6 and 2, particularly in the rapidly evolving cases.

B. *Cases Without Preceding Trauma*

Chronology and prognosis. In non-traumatic cases, obviously one can only study the duration of the symptomatic phase. The upper half of fig. 7 indicates that these

Symptomatic phase

	0 h	0-6 h	6-24 h	1-3 d	3-7 d	1-2 w	2-4 w	1-3 m	3-6 m	>6 m
>6 m										
3-6 m										
1-3 m										
2-4 w	1			1					1	
1-2 w							1			
3-7 d					2			1		
1-3 d				2	1			1		
6-24 h										
1-6 h		1								
0-1 h	8	2	1	1				1		

Asymptomatic phase

FIG. 6. Number of patients who died without brain contusion. Mortality independent of associated brain injury. Note relative rarity of this possibility especially in rapidly evolving cases.

cases seem to segregate into two populations. There is a small group of 8 patients admitted within six hours after the onset of signs and symptoms who had a poor outcome: only 2 of them survived. It is clear from Table I that one should not describe the first group as being 'acute spontaneous subdural hæmatoma', if the term 'spontaneous' is used in the sense of 'without apparent cause'; a great variety of ætiological factors may have contributed to the genesis of the subdural hæmatoma and among these, anticoagulants play the most important role. The most appropriate designation appears to be 'acute non-traumatic subdural hæmatoma'. A second larger group of 42 patients was admitted more than twenty-four hours after the onset of manifestations, and had a relatively good prognosis.

The second group largely conforms to the conventional concept of 'chronic subdural hæmatoma', although many physicians will hesitate to call a case chronic if the symptoms have been present for only twenty-four hours. They prefer the designation 'non-acute'.

In conclusion, in the group without trauma there is a clear difference in outcome between patients who were admitted within six hours of the onset of symptoms, and those in whom this interval was more than one day. Accordingly, the combination of chronological and prognostic criteria does offer a basis for classification.

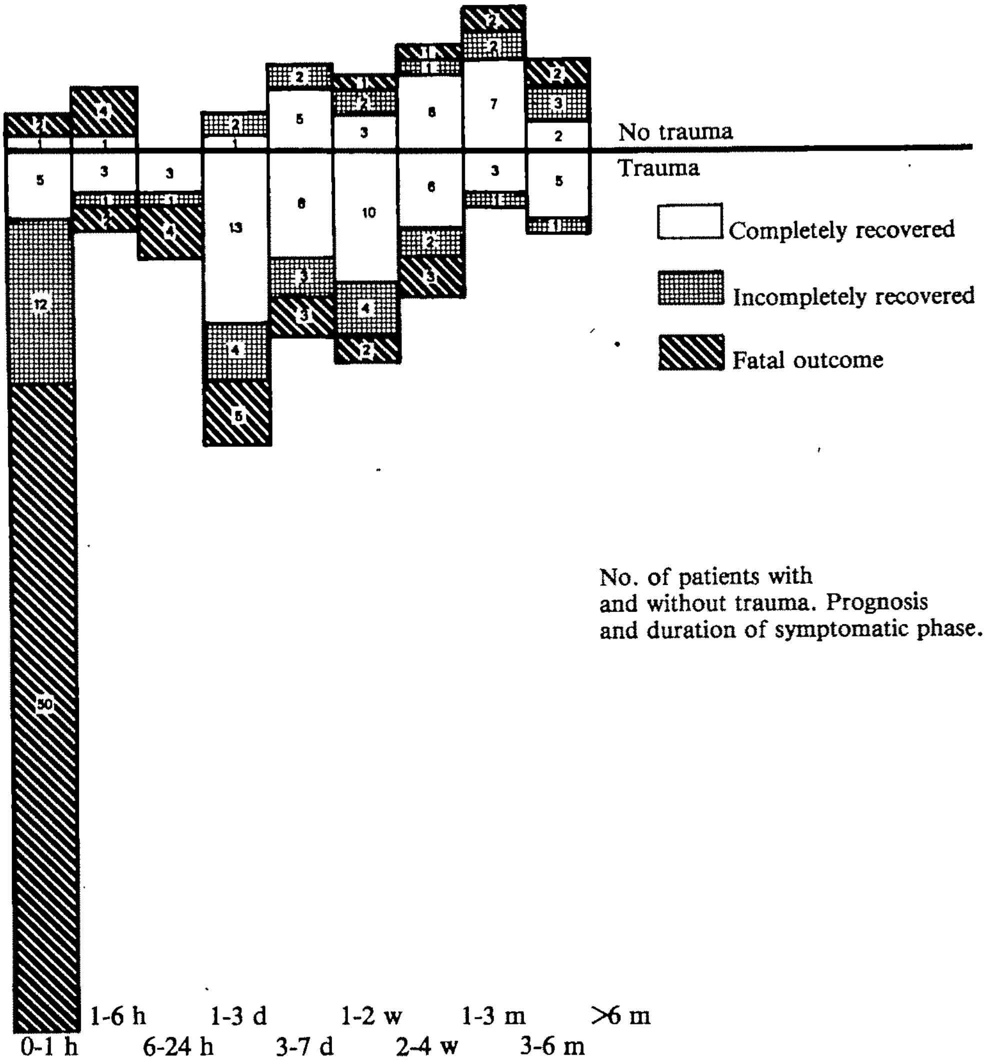


FIG. 7. Presence or absence of trauma, duration of symptomatic phase and prognosis. Note continuity of traumatic cases (*lower half*) and discontinuity of non-traumatic cases (*upper half*) after 6 hours duration

Traumatic and non-traumatic subdural hæmatoma. It is a generally held opinion that there is no fundamental difference between chronic traumatic subdural hæmatoma and chronic subdural hæmatoma without trauma, because the clinical manifestations and appearance at operation are similar.

Authors who comment on this point (Trotter, 1914; Logue, 1951) assume that a subdural hæmatoma may be caused by a very slight trauma which the patient may have forgotten. This assumption virtually denies the existence of non-traumatic subdural hæmatoma and it cannot be proven or disproven.

TABLE 1. PATIENTS WITHOUT PRECEDING TRAUMA AND ADMITTED WITHIN SIX HOURS AFTER THE ONSET OF SYMPTOMS

Sex	*Age (yrs)*	*Symptoms*	*Ætiological factors*	*Outcome*	*Source*	*Fresh/old clot*
M	58	Sudden headache and coma	Anticoagulants	Died	Venous	Fresh
M	44	Sudden illness, vomiting, coma	Hypertension	Recovered	Unknown	Fresh
F	51	Sudden coma	Hypertension Aneurysm int. carotid artery	Died	Aneurysm	Fresh
M	65	Sudden headache, vomiting, coma	Anticoagulants	Recovered	Unknown	Fresh
M	49	Sudden coma	Anticoagulants	Died	Unknown	Fresh
M	72	Sudden coma	Anticoagulants Lumbar puncture 2 d previously	Died	Unknown	Fresh
M	56	Sudden headache, loss of consciousness within 1 h	Anticoagulants Abuse of alcohol	Died	Unknown	Fresh
F	48	Sudden coma; disorientated since craniotomy 5 wks previously	Anticoagulants Craniotomy for chromofobe adenoma	Died	Unknown	Old

If the notion of ætiological identity of chronic traumatic subdural hæmatoma and chronic subdural hæmatoma without trauma is correct, one would expect a similarity in distribution of cases with respect to duration of symptoms and outcome. However, no symmetry of distribution of these parameters is seen (fig. 7): the traumatic group clearly contains more cases with a shorter symptomatic phase and a higher mortality rate. Moreover, the fatal outcomes that do occur in the non-traumatic group are restricted to patients with a symptomatic phase of more than one week. If differences in distribution of cases with symptomatic phases exceeding twenty-four hours are analysed statistically these differences are found to be significant ($P < 0.01$, Kolnogorov-Smirnov two sample test, Siegel, 1956). The differences in mortality rates related to duration of the symptomatic phase are also significant ($P < 0.05$, test on equality of logistic regression slopes, Armitage, 1971). The factors causing these differences are elusive. However, as can be seen in fig. 8, at least some of the differences are accounted for by the proportion of cases with associated brain injury. The latter, as shown above, carries a grave prognosis and therefore accounts for the poor outcome in the cases with a short symptomatic phase.

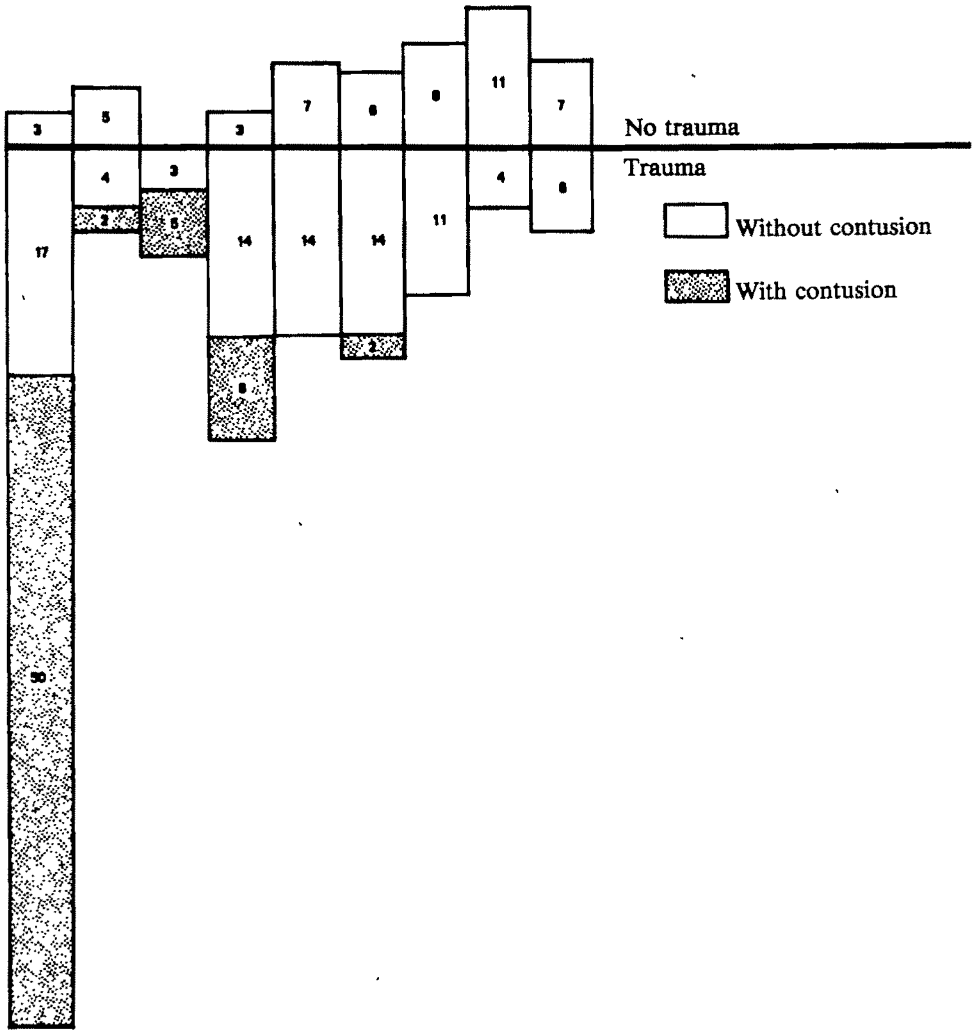


FIG. 8. Presence or absence of trauma, duration of symptomatic phase and associated brain injury. Note better symmetry with regard to abscissa after subtraction of cases with associated brain injury. Indication of time elapsed identical to that in fig. 7.

DISCUSSION

The present study provides a means of avoiding several pitfalls of current terminology. A review of the pertinent literature on subdural hæmatoma reveals that the terms 'acute' and 'spontaneous' in particular are used in both an arbitrary and an ambiguous way. 'Acute' has been defined as 'with evidence of unhealed or acute brain injury' (Munro, 1942), as 'leading to death or operation within fourteen days after trauma' (Logue, 1951) or as 'presenting urgent symptoms within three days after trauma' (McKissock *et al.*, 1960), to give three illustrations of arbitrary usage. In non-traumatic cases, 'acute' has been defined as 'presenting as cerebrovascular accident' (Scott, 1949), or as 'with abrupt onset of headache or loss of consciousness' (Talalla and McKissock, 1971). As the latter authors included patients who had suffered headaches for up to two months prior to the abrupt onset of symptoms, this also illustrates ambiguous usage because the term 'acute' may apply to the disorder as a whole, or to one particular symptom of an essentially chronic case. The term 'spontaneous' is used by Scott (1949) to mean 'non-traumatic' and 'without apparent cause'; by Talalla and McKissock (1971) in the sense of 'due to spontaneous rupture of an artery' and of 'without apparent cause'. O'Brien, Norris and Tator (1974) also used the term 'spontaneous' to describe cases with recent trauma. With regard to the terms 'traumatic' and 'non-traumatic', it is obvious that the difference is irrelevant to those who consider the presence of, perhaps slight, trauma axiomatic (Trotter, 1914; Munro, 1942; Logue, 1951; McKissock *et al.*, 1960).

The present series, however, suggests that despite an obvious clinical resemblance between traumatic and non-traumatic chronic cases, significant differences do exist, and this suggests that the factors determining their genesis and further development are of a different nature.

On the basis of findings obtained on analysis of a series of 212 cases, the following terminology for classification of subdural hæmatoma is proposed.

A. *Subdural Hæmatoma following Trauma* (fig. 7, lower half)

An arbitrary subdivision might be made into acute, subacute and chronic. With the aid of figs. 1–6, one can estimate roughly where the optimal boundaries between these groups should be, with respect to expected numbers of patients, outcome and rate of associated cerebral injury. The chronological site of these boundaries can be chosen depending on the type of study or description.

B. *Subdural Hæmatoma without Preceding Trauma* (fig. 7. upper half and Table I)

Such cases can be divided into two groups: (1) acute and (2) non-acute or chronic.

(1) *Acute* is defined as presenting with sudden symptoms of great severity, and resulting in hospital admission within six hours. This condition is rare, apparently has a variable ætiological background and carries a grave prognosis. There is a high probability that it will be mistaken for 'stroke'.

(2) *Non-acute or chronic* cases are admitted one day to six months after the onset of symptoms. The prognosis is relatively good.

This classification is based upon material from Leyden University Hospital. Although populations of patients with subdural hæmatoma may differ somewhat according to geographic and socio-economic factors, it does not seem likely that the present material would differ substantially from that of other hospitals in densely populated urban areas.

SUMMARY

A retrospective study of 212 cases of subdural hæmatoma has been carried out in an attempt to find a basis for classification and to propose a useful terminology. It is argued that a subdural hæmatoma should be considered as traumatic when preceded by a trauma in the sense of a 'morbid condition of body produced by wound or external violence'.

The present series contained 154 cases with and 50 cases without preceding trauma. The 154 traumatic cases were categorized according to the durations of their asymptomatic and symptomatic phases, that is the chronological criterion. It was found that the material represented a full spectrum of manifestations without natural boundaries. Combining the chronological criterion with the criteria 'outcome' and 'associated brain injury' did not improve perspectives for a useful classification. The 50 non-traumatic cases, on the other hand, could be subdivided into acute (8) and non-acute or chronic (42), the acute cases presenting with severe symptoms within six hours after sudden onset, and carrying a poor prognosis. Cases presenting from one day to six months after the onset of symptoms may be referred to as non-acute or chronic and have a relatively good prognosis.

Comparison of outcome of traumatic and non-traumatic cases with symptomatic phases exceeding twenty-four hours suggests that these groups, despite their clinical and pathological similarities, have different ætiological backgrounds.

ACKNOWLEDGEMENTS

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A GRAB REFLEX IN THE HUMAN HAND

by M. M. TRAUB, J. C. ROTHWELL *and* C. D. MARSDEN

(From The University Department of Neurology, Institute of Psychiatry and King's College Hospital Medical School, London SE5 8AF)

INTRODUCTION

WHEN a subject performing a simple tracking task meets with a sudden increase in load, short- and long-latency automatic electromyographic (EMG) responses are elicited, followed by such voluntary effort as is required to completely overcome the obstruction. Although the function and importance of the automatic EMG events has been debated, they do produce force to compensate or partly compensate for the added load.

The usual experimental situation employed to demonstrate these phenomena has been to oppose or reverse the movement undertaken by the subject so as to stretch the muscle executing the movement. Marsden, Merton and Morton (1972, 1976), for example, extensively studied the effect of interfering with movement of the top joint of the thumb by changing the force applied to the thumb pad so as to stretch or otherwise interfere with the contraction of flexor pollicis longus. We now investigate the effect of *indirectly* changing the length of flexor pollicis longus, while tracking with the top joint of the thumb, by applying sudden pulls or releases to the wrist rather than to the thumb itself.

When the long thumb flexor is unloaded *indirectly* an increase in EMG activity of flexor pollicis longus occurs, not the expected decrease. However, this paradoxical response to muscle shortening maintains the thumb pad on target. The response is not solely a reaction to the pull on the wrist, for it occurs only when the thumb is displaced from the beam on which it presses, and does not appear when the subject tracks on a transducer held free in the hand.

Releasing the wrist, which *indirectly* stretches the long thumb flexor, causes not only a typical reflex burst of EMG activity in flexor pollicis longus, but also an early, subsequent, *indirect* silence.

An automatic flexion response also is elicited following pulls or releases to the wrist, if a subject maintains his thumb and index finger a few millimetres from the rim of a full glass of sherry. In this instance there is no change in sensory input to the thumb or to the long thumb flexor.

It appears that this response in flexor pollicis longus to disturbances of the arm is a 'grab reflex' which is subtly adapted to the task the subject is performing.

METHODS

A view of the apparatus is shown in fig. 1A. The subject stood facing a table, to the front edge of which was attached a Grass FT 10 force-displacement transducer at about waist height. Behind the transducer was a low inertia torque motor (Printed Motor Ltd., Type G12M4), with a 7 cm diameter pulley connected to its spindle. The subject's semipronated right arm pointed vertically downwards and was attached to the pulley *via* a short chain to the wrist. The equipment was adjusted so that an increase in motor torque pulled the arm forward. The subject was asked to flex the top joint of the thumb against the force transducer. The resulting displacement of the transducer arm deflected the lower beam of a Tektronix D10 oscilloscope placed 70 cm in front of the subject. Displacement of the transducer arm by 0.2 mm moved the lower beam by 1 cm from left to right. The subject had to match this lower beam with an upper beam moving from left to right at 10 deg/s every ten seconds. When the transducer arm had been displaced by about 1 mm (equivalent to a force of 1.5 N), the output 'activated' a PDP 12 computer by means of a Schmitt trigger with a random delay of 0–150 ms. In a subsidiary set of experiments subjects were asked simply to maintain a constant degree of flexion against the force transducer without reference to the visual tracking task and perturbations were given to the wrist at random intervals between 5 and 6.5 s. Data was collected and averaged from four input channels over a 250 ms epoch using the programme AV4X4 (Mr H. B. Morton). Thirty-two or forty trials were averaged into four or five separate groups of eight, selected by the computer in pseudorandom order. In one group (the controls) the standing motor force of 1.7 N did not change, but in the other three groups the torque changed suddenly 50 ms after the computer was triggered to 2.9 or 4.3 N (wrist pulls), or to 0.85 N (wrist releases). The exact time of movement of the arm was detected by a Vibrometer sa 105 accelerometer strapped over the radial border of the forearm.

In certain experiments the subject flexed the top joint of the thumb against a second torque motor. The thumb pad bore on a crank arm attached to the motor spindle, the force exerted being measured by a pair of semiconductor strain gauges (Pye Dynamics, type 3A/1A/350) mounted above and below the arm. Sudden torque changes could be introduced by this second motor rather than by the wrist motor, so as to compare the EMG responses of flexor pollicis longus to direct thumb perturbations with those caused indirectly by pulls to the wrist.

EMG activity was recorded using 1 cm diameter silver-silver chloride disc electrodes placed over the belly of flexor pollicis longus 8 and 12 cm from the wrist crease. By carrying out ballistic movements of the fingers and hand we showed that there was little cross-talk from other muscles. In two of the authors (J.R. and M.T.) localization of the response was confirmed by means of a pair of 3/1000-in diameter platinum iridium wire electrodes inserted into flexor pollicis longus. The EMG was pre-amplified by a Devices 3160 pre-amplifier with a time constant of 20 ms, low pass filtered to attenuate the signal by 3 dB at 2.5 kHz and was then amplified by a Devices 3120 amplifier. The signal was full-wave rectified and integrated by a Devices signal processor type 4016. The angular position of the torque motor was measured by means of a sensitive Bourns 2-in servo potentiometer attached to the shaft.

Anæsthesia

In order to investigate the mechanism of the EMG response of flexor pollicis longus to wrist perturbations, experiments were carried out to anæsthetize different parts of the right arm of two of the authors (J.R. and M.T.). The skin of the wrist underneath the chain was rendered insensible by repeated subcutaneous injections of 3 ml plain 1 per cent lignocaine. This unpleasant procedure required about fifteen insertions of the hypodermic needle. Thumb anæsthesia was achieved by digital block at the base of the thumb using 3 ml of plain 1 per cent lignocaine. The motor point of flexor pollicis longus was localized by surface electrical stimulation (Lance and de Gail, 1965) and then anæsthetized by the intramuscular injection of 3 ml of plain 1 per cent lignocaine. This manœuvre did not appreciably interfere with voluntary power in flexor pollicis longus, but markedly reduced its

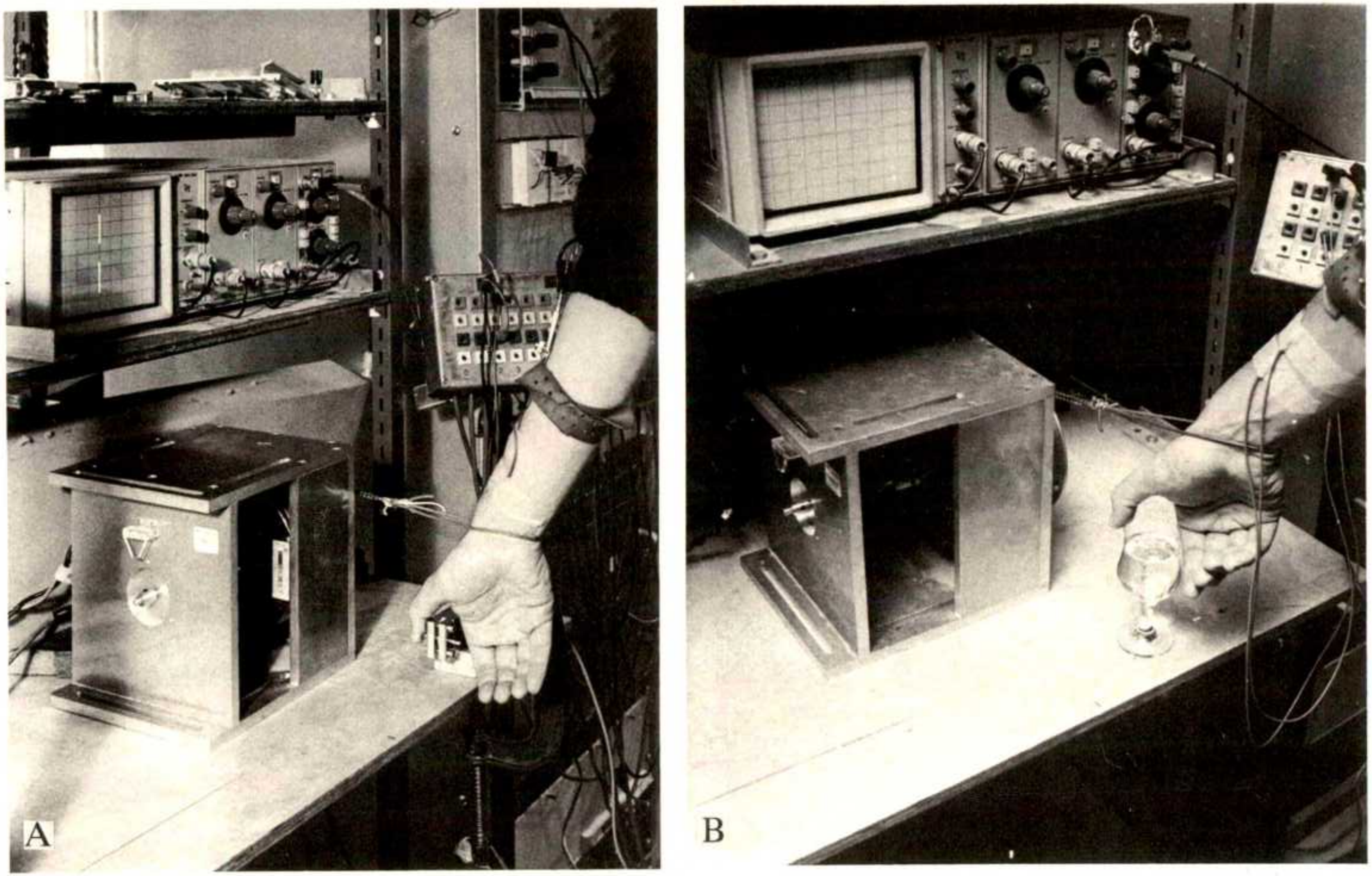

FIG. 1. A, apparatus used for investigating the responses of flexor pollicis longus to indirect task disturbances produced by pulling on the wrist. The thumb pad pressed on the lever arm of a small force/position transducer (Grass FT10) and its position was displayed on the oscilloscope screen. The fingers were held lightly flexed, well out of the way of the body of the transducer. A low inertia electric motor (Printed Motors Ltd., type G12M4) was attached to the wrist *via* a short chain and wire loop. Also visible are the silver cup surface electrodes stuck down with adhesive tape over the lower belly of the flexor pollicis longus muscle, and the earthing electrode. B, the posture employed in obtaining the 'sherry-glass' response.

long-latency EMG response to stretch elicited by the methods of Marsden *et al.* (1976). Motor point anæsthesia of flexor pollicis longus always caused slight paræsthesiæ in median nerve distribution so we repeated the experiments using the ring finger to track; injection of 3 ml plain 1 per cent lignocaine into the appropriate motor point of flexor digitorum profundus caused no cutaneous sensory change.

Subjects

All the illustrations shown in this paper are of experiments performed on two of the authors (J.R. and M.T.). All our findings, however, except for those involving the injection of local anæsthetic, were confirmed in eleven other normal volunteers.

RESULTS

Although pulls and releases were presented to the wrist in pseudorandom order together with controls, the response of flexor pollicis longus to each stimulus is discussed separately.

Response of Flexor Pollicis Longus to Wrist Pulls

If the wrist was pulled forwards while the thumb was being actively flexed against the fixed force transducer, the thumb pad was pulled away from the lever. This reduced the force opposing the contraction of flexor pollicis longus so that the thumb flexed and the muscle passively shortened. In other words, flexor pollicis longus was unloaded *indirectly* by a pull to the wrist. About 50 ms after the wrist pull, a sharp increase of EMG activity in flexor pollicis longus occurred (fig. 2). Although the response usually was elicited during a thumb tracking task, an identical event was observed when the subject maintained a constant force of thumb flexion and received disturbances to his wrist every 5 to 6.5 seconds.

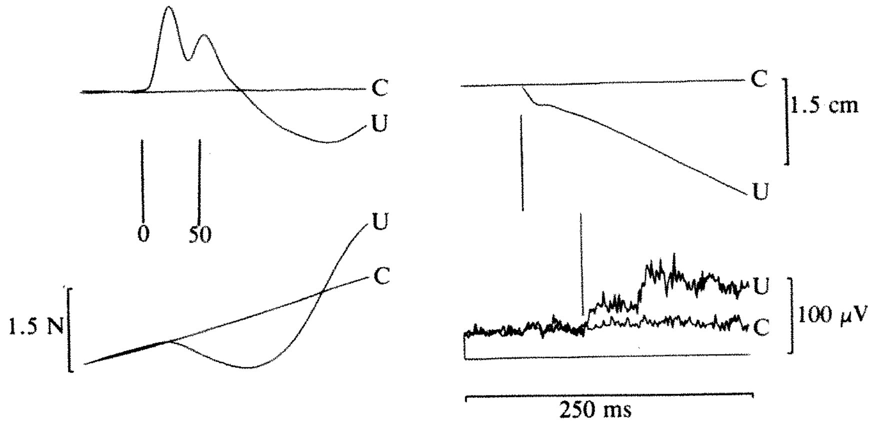

FIG. 2. The response of flexor pollicis longus to indirect unloading produced by a pull to the wrist (U). The upper traces show linear acceleration of the wrist (*left*) and motor position (*right*). Lower traces show the force exerted by the thumb on the transducer (*left*) and the rectified EMG from flexor pollicis longus with its zero level (*right*). The results of control run (C) when no perturbations were given are superimposed on the response to wrist pulls (U), which were interspersed randomly. Each trace is a grand average of 80 control and 80 wrist pull trials. The timing bars are at the time of the motor pull and 50 ms later.

It was impossible to eliminate the response by instructing the subject to relax voluntarily on perceiving the wrist pull. Only 1 out of 6 subjects proved able to decrease the early automatic response and then only by some 10 per cent, whilst the other subjects were able to depress EMG levels only at very long latencies (over 120 ms). The effect of voluntary set on the response also was investigated by asking 6 subjects to flex the thumb hard on feeling the pull to wrist, which they found considerably easier. The percentage increase in size of the first 25 ms of the response to wrist pulls produced by this instruction averaged 39 per cent (± 12 per cent, 1 SE), a change comparable to the effect of the same instructions on the direct thumb stretch reflex (*see* Marsden, Merton, Morton, Adam and Hallett, 1978).

Fig. 2 shows a second discrete burst of EMG activity starting 100 ms after the pull to the wrist, a pattern that was found in 3 out of 11 subjects. Although it might be regarded as voluntary, none of these subjects could abolish it by effort of will.

The size of the early automatic response to wrist pulls increased as the stimulus was made larger, but details of this relationship were not investigated.

Direct unloading of flexor pollicis longus during active thumb flexion led to the opposite response, namely, the classical silent period described by Angel, Eppler and Iannone (1965) and by Marsden, *et al.* (1976). Fig. 3B shows that there was a decrease in EMG activity in flexor pollicis longus about 50 ms after the muscle had

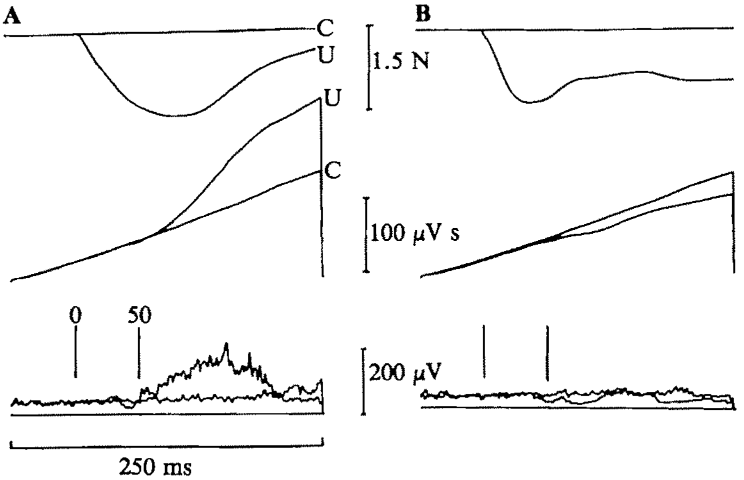

FIG. 3. Comparison of the response of flexor pollicis longus to *indirect* unloading produced by a pull to the wrist (A), and *direct* unloading produced by reducing the force opposing the tracking thumb (B). In both experiments the thumb tracked against the lever arm of a second torque motor. In A, the motor arm was clamped to prevent it moving and the subject tracked using the force transducer output from the lever. Pulls (0.2 Nm) were given to the wrist in random trials which lifted the thumb off the lever. In B, the motor arm was free to move and the subject tracked using the motor position output which also triggered the computer. A steady torque was exerted by the wrist motor throughout, but on random trials the thumb motor torque was reduced from 0.08 Nm to 0.04 Nm. The background torque (0.08 Nm) produced approximately the same force on the thumb as the triggering lever in A. The *top* traces show the force output from the thumb lever arm, the *middle* pair of traces show the integrated EMG from flexor pollicis longus, and the *lower* pair show rectified EMG with its baseline. Each trace is a grand average of 48 unloading trials (U), with appropriate controls (C). Groups of direct and indirect unloading were performed alternately. Timing lines are shown at the onset of change in motor torque and 50 ms later.

been *directly* unloaded by a reduction in the force offered to the thumb, in contrast to the increase in EMG seen when flexor pollicis longus was indirectly unloaded by a pull on the wrist (fig. 3A).

Change of Gain with Load

The effect of different thumb tracking forces on the size of the EMG response in flexor pollicis longus to wrist pull was investigated. The tracking forces ranged from 0.5 N to 5 N. The size of the response to any given pull on the wrist was found always to be a constant fraction of the basal level of EMG activity. Marsden *et al.* (1972) termed this phenomenon 'gain control' in their description of the *direct* stretch reflex in the long thumb flexor. The existence of gain control also in the *indirect* response allowed the comparison of results with different levels of background EMG, for by applying a scaling factor all control-integrated EMG records could be aligned to the same slope. A change in basal EMG levels was inevitable after such procedures as thumb anæsthesia (*see* Marsden, Rothwell and Traub, 1979).

Response of Flexor Pollicis Longus to Wrist Releases

When the force applied to the wrist was reduced, the arm moved back so that the pressure on the thumb pad was increased and flexor pollicis longus was passively stretched. If the subject tracked against a fixed force transducer (fig. 4A) there was an

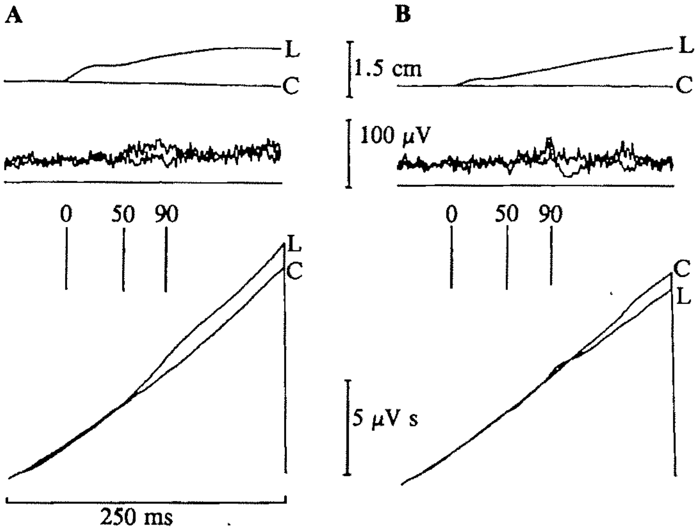

FIG. 4. The response of flexor pollicis longus to indirect stretch produced by unloading the torque to the wrist. In A, the thumb was tracking against a fixed force transducer, causing a large thumb stretch when the wrist was released. In B, the thumb pressed against a lever attached to a second motor which exerted a constant force approximately equal to the force trigger lever in A, causing a small thumb stretch when the wrist was released compared with A. In B, the subject used the position output from the thumb motor as tracking spot. Traces show wrist motor position (*top*), rectified EMG (*middle*) and integrated rectified EMG (*bottom*). Results are the grand averages of 48 trials (L) with appropriate controls (C). Experiments using condition A were performed alternately with those using condition B. Timing lines are shown at the onset of change in wrist motor torque, and 50 ms and 90 ms later.

increase in flexor pollicis longus EMG activity 50 ms after the wrist release and not the decrease expected from the results of pulls to the wrist. However, this response was much briefer than the burst of activity produced by a pull to the wrist showing a return to basal levels after 90 ms. This short-lived increase in flexor pollicis longus EMG activity was probably a response to *direct* muscle stretch (*see* Marsden *et al.*, 1976). Indeed, in fig. 4B are illustrated the results of an experiment in which the subject tracked against a low inertia torque motor offering the same force as the fixed transducer. When the wrist was released in this situation the thumb was stretched much less because it moved the motor and this caused a very much smaller and later increase in flexor pollicis longus EMG followed by a decrease at about 90 ms.

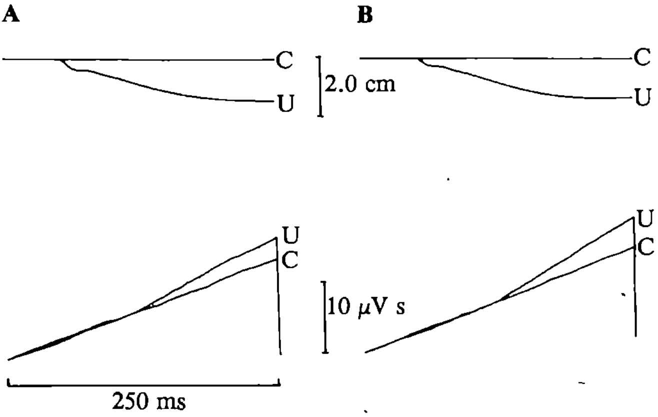

FIG. 5. Effect of wrist anæsthesia on the response to wrist pulls. A shows the normal responses prior to anæsthesia and B shows the responses after anæsthesia of the skin of the wrist. The *upper* traces show wrist motor position; the *lower* traces show the rectified and integrated EMG from flexor pollicis longus. Each trace is the grand average of 32 trials (U) and 32 controls (C) performed in four groups.

The Nature of the Adequate Stimulus for Indirect Responses

Fig. 5 shows that the response to wrist pull was unaffected by anæsthesia of the skin underneath the wrist chain. The response to wrist release was also unaltered (not illustrated). These events are not long-latency cutaneous reflexes (for example, Stephens and Usherwood, 1976). The response to wrist pull may have been due to transmitted vibration caused by the motor jerk directly exciting spindles in flexor pollicis longus (*see* Lance and de Gail, 1965). However, motor point anæsthesia of flexor pollicis longus markedly reduced its direct response to stretch (fig. 6A) without affecting the response to wrist pull which indirectly unloaded the thumb (fig. 6B), suggesting that it was not elicited by a local muscle stimulus. The response to wrist release was reduced (fig. 6C) in keeping with the proposition that it was a *direct* stretch reflex.

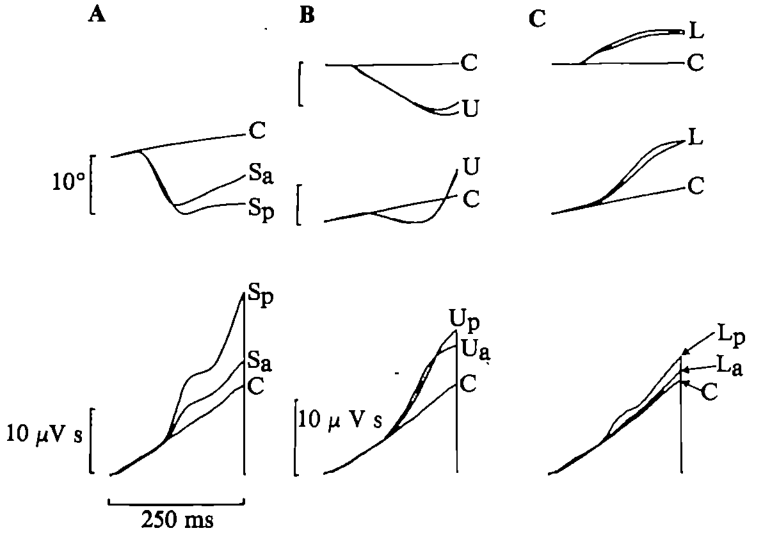

FIG. 6. The effect of motor point anæsthesia on the response of flexor pollicis longus to A, direct stretch (S); B, pulls to the wrist (U); C, releases of the wrist (L). In A the thumb tracked against a second torque motor, using its positional output. Direct stretches were produced by increasing motor torque from a background of 0.1 Nm to 0.24 Nm. The *upper* traces are motor position, the *lower* traces integrated EMG. In B and C the subject tracked in the normal way against a fixed force transducer and perturbations were given to the wrist, which was pulled by increasing wrist motor torque from 0.12 Nm to 0.3 Nm, or released by decreasing wrist motor torque from 0.12 Nm to 0.06 Nm. Traces are wrist motor position (*top*), force transducer output (*middle*) and integrated EMG (*bottom*). In all traces a control trial (C) is superimposed on the response before (p) and after (a) injection of local anæsthetic into the motor point of flexor pollicis longus. Each trace is the grand average of 48 trials performed in six groups. The integrated EMG records after anæsthesia have been scaled up by a factor of 1.7 to match initial slopes with the preceding trials. The anæsthetic had to be injected directly beneath the surface electrodes, which reduced the EMG signal.

The response to wrist pull may have been driven by input derived from receptors in proximal muscle or joint. This conclusion was supported by the experiments illustrated in fig. 7. When the experimenter firmly held on to the subject's arm to minimize its movement, the response of flexor pollicis longus to a pull on the wrist was substantially diminished (this experiment also provided further evidence that the response was not a cutaneous reflex).

Holding the arm not only decreased movement at proximal joints but also prevented the change in pressure on the thumb pad so that its success in decreasing the response of flexor pollicis longus might be interpreted as indicating that this response was due to the stimulus evoked at the thumb by the arm movement. However, thumb anæsthesia did not affect the response to wrist pulls (fig. 8A) although it did decrease the early part of the response to wrist release (fig. 8B), in keeping with the known effect of thumb anæsthesia on the *direct* stretch reflex (Marsden *et al.*, 1977).

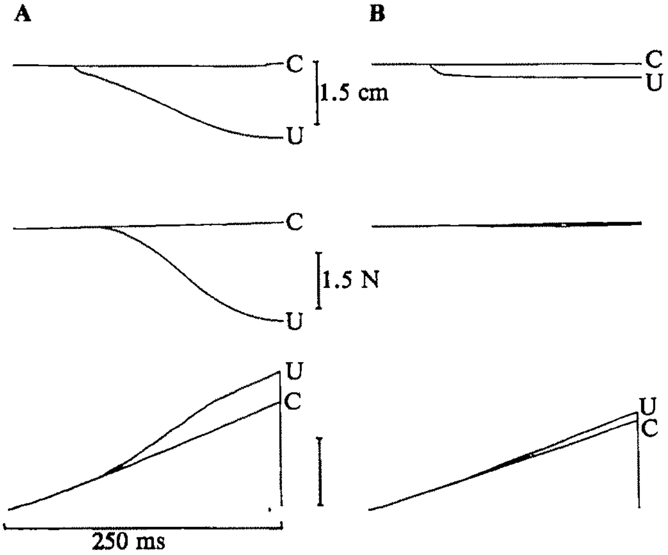

FIG. 7. Effect of restricting arm movement on the response of flexor pollicis longus to pulls on the wrist while tracking against a force transducer. Groups of trials were alternated between A, normal tracking and B, with the right arm strongly braced by the experimenter to limit movement caused by the motor pull. The traces are wrist motor position (*above*), force transducer output (*middle*) and rectified, integrated EMG from flexor pollicis longus (*below*). Each trace is a grand average of 48 wrist pull trials (U) performed in six groups, along with randomized control runs (C).

Effect of Wrist Pulls on Other Muscles

The flexion response to wrist pulls was not restricted to the long thumb flexor. Wire electrodes inserted into flexor digitorum profundus recorded a simultaneous burst of activity in this muscle evoking flexion of all the digits.

When the arrangements were altered so that the thumb was actively extended against the force transducer, the expected *direct* response to stretch and release of the extensor pollicis longus always was evoked by disturbance to the wrist. Therefore the *indirect* response to wrist pulls was a property of the thumb and finger flexor muscles.

Effects of Pulls to Other Parts of the Body

A flexion response was evoked in the long thumb flexor with a latency of 70 ms when the subject was pulled at the waist (with forces of between 5 N and 8.5 N on a background force of 2 N). This increase in latency compared to the response to the usual wrist disturbance is partly attributable to the difference in inertia of the parts being pulled. However, in 6 out of the 11 subjects a flexion response in flexor pollicis longus also was elicited with a latency of 65 ms to 70 ms after pulls of usual size to the contralateral wrist. In this instance the increase in latency of the flexion response may be explained by an increase in the time taken for central processing.

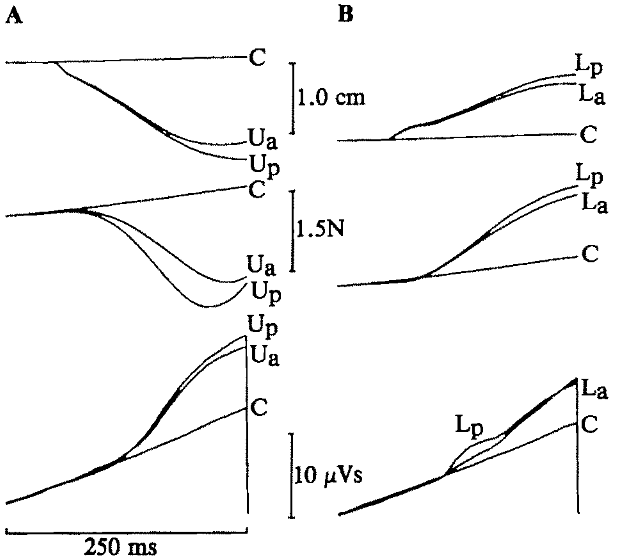

FIG. 8. Effect of thumb anæsthesia on the responses to A, wrist pulls, and B, wrist releases. In each set of traces three types of trial are superimposed; unanæsthetized, unperturbed control (C), unanæsthetized perturbed (wrist pull-U_p; wrist release-L_p) and anæsthetized perturbed (wrist pull-U_a; wrist release-L_a). The traces were wrist motor position (*above*), thumb force transducer output (*middle*) and rectified integrated EMG from flexor pollicis longus (*below*). Each trace is the grand average of 48 runs. The rectified and integrated EMG records after thumb anæsthesia have been scaled down by a factor of 1.5 so that the initial slopes are equal. This increase in EMG activity after thumb anæsthesia has been described in detail elsewhere (Marsden *et al.*, 1979).

Pulls to the ipsilateral wrist always evoked the usual stretch reflex in proximal arm muscles whilst pulls to the waist or contralateral wrist produced changes in activity which were restricted to the flexors of the thumb and digits. Such a limitation of activity to certain muscle groups contrasts with the pattern exhibited in a startle response and also demonstrates that the flexor response in the thumb and fingers is not necessarily part of a generalized postural reaction in the upper limb.

Effect of Wrist Pulls with the Transducer Held Free in the Hand

Subjects were asked to track on the transducer whilst they held it free in their hand rather than being fixed to the table. In these circumstances wrist perturbations no longer displaced the thumb from the lever and no response to wrist pull was evident in flexor pollicis longus (fig. 9). This was not the result of some inhibitory signal coming from pressure centres in the palm since holding another object in the hand whilst tracking in the normal way against the fixed transducer had no effect on the muscle response to wrist pull. Complete suppression of the response, however, seemed to be partly dependent upon the tracking task, for when the subject was requested to maintain a constant degree of thumb flexion against the transducer a very small and labile burst of EMG activity occurred with a latency of 50 ms and lasted only some 15 ms.

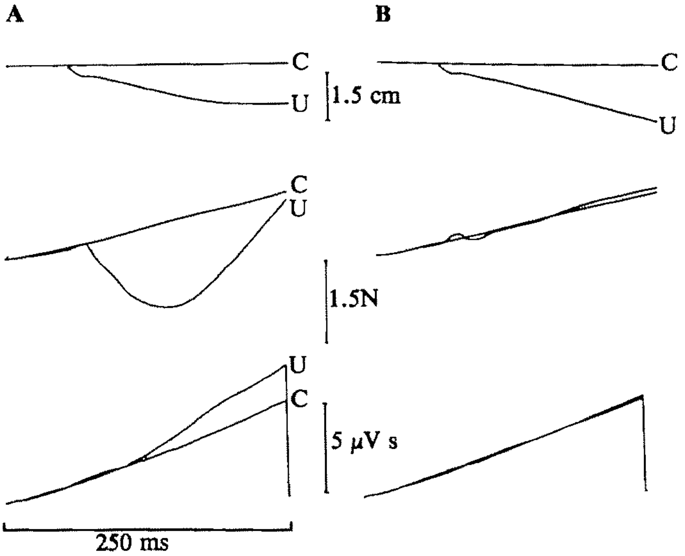

FIG. 9. The effect of the task on the response to wrist pulls. In A, the thumb tracked normally against a fixed force transducer. In B, the subject held the force transducer in his hand. The traces are wrist motor position (*above*), thumb force transducer output (*middle*) and rectified, integrated EMG from flexor pollicis longus (*below*). Each pair of traces consists of a superimposed control (C) and the response to a motor pull (U). Each trace is the grand average of 48 trials. Groups were alternated between conditions A and B.

'*Sherry-glass Experiment*'

In the experiments outlined so far the tracking task was firmly fixed, so the thumb and finger flexor response could have been part of a postural steadying reaction. In a further series of experiments the same wrist disturbances as before were given while subjects were asked to maintain their thumb and index finger a few millimetres from the rim of a full glass of sherry as if they were about to pick it up (*see* fig. 1B for the rather strange posture involved).

Fig. 10A shows that pulls to the wrist evoked the usual burst of EMG activity in flexor pollicis longus, but wrist release also caused an increase, which now could not be attributed to *direct* muscle stretch. Indeed, neither the response to wrist pull nor that to wrist release in these circumstances was affected by anæsthesia of the hand or of the motor point of flexor pollicis longus (not illustrated). Fig. 10B shows that no such response was seen when the subject received the same disturbances to the wrist while flexing his thumb against a small block of wood held in the palm of the hand. However, a small labile EMG burst sometimes occurred at a latency of 50 ms which varied between subjects and in the same subject from day to day (not illustrated).

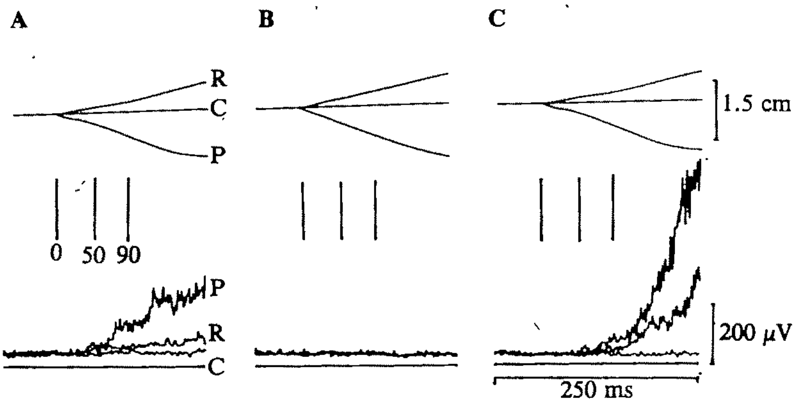

FIG. 10. The 'sherry-glass' response in flexor pollicis longus. In A, the subject maintained his thumb and index finger near the rim of a sherry glass (*see* fig. 1B) and disturbances were applied to the wrist. In B he flexed his thumb against a small block of wood held free in the palm of his hand and disturbances were applied to the wrist as in A. In C an upright block of wood was substituted for the sherry glass and the subject was instructed to flex his thumb voluntarily as rapidly as possible on perceiving the disturbance to the wrist. Traces show motor position (*top*) and rectified EMG (*bottom*). Each set of traces is the superimposed grand average of 48 control (C), motor pull (P) and motor release (R) trials. Timing bars set at the time of the disturbance (0), 50 ms and 90 ms later.

The 'sherry-glass' response could not be substantially increased by effort of will. Fig. 10C was performed with an upright block of wood substituted for the brittle sherry glass and demonstrates that the voluntary burst of EMG activity followed the automatic 'sherry-glass' burst by some 40 ms. The 'sherry-glass' response, although not voluntary, was dependent on the subject's intent, for if he chose to ignore the fragility of the glass and knock it over, no response was observed.

DISCUSSION

When flexor pollicis longus was indirectly unloaded by a pull to the wrist, there followed an automatic increase in EMG activity after some 50 ms, not the decrease seen when the muscle was unloaded directly. Since this response to wrist pull was not affected by anæsthesia of the thumb, of the skin of the wrist or of the motor point of the long thumb flexor, it is suggested that it was driven by a stimulus to proximal muscles or joints. (On the other hand, the burst of EMG activity in flexor pollicis longus produced by releasing the wrist, which indirectly loaded the muscle, was presumably a direct stretch reflex as it was reduced by anæsthesia of the thumb or of the motor point of the long thumb flexor (Marsden *et al.*, 1977)).

The indirect response of flexor pollicis longus to unloading was elicited only when the wrist pull removed the thumb from its target; it disappeared if the tracking task was held free in the hand. This change was immediate, occurring on the first new trial, so was not the result of some form of habituation, as has been described, for example, with noxious skin reflexes (Hagbarth and Kugelberg, 1958) or during adaptive learning, as in the reversal of the vestibulo-ocular reflex of subjects wearing inverting prisms (Gonshor and Melvill Jones, 1973). A more closely related example of such immediate reflex modifications was described by Nashner and Wolfson (1974) who showed that the reflex in gastrocnemius produced by galvanic stimulation of the human labyrinth was distorted by neck position. A stimulus that elicited a burst of activity in the calf muscles with the head turned to the right caused inhibition of the same muscles when the head was rotated through 180 degrees. Presumably there is interaction between vestibular input and information from neck proprioreceptors to effect an appropriate stabilizing response in triceps suræ, no matter what the head position.

In the case of the response of the long thumb flexor to wrist pull the mechanism of adaptation to circumstance is not clear. When the tracking task was held in the hand, changes in thumb pressure or flexor muscle length no longer occurred, yet the normal indirect response was not affected by interrupting afferent input from the thumb or from flexor pollicis longus by local anæsthesia. The flexibility of the response to *indirect* unloading of the muscle with subtle changes in context is of a degree normally associated with voluntary events but it was not modified substantially by effort of will. In fact, we cannot state at which level in the central nervous system the change occurs or even the source of the afferent input upon which this modification depends.

In some respects the response to *indirect* unloading of flexor pollicis longus is similar to the anticipatory postural reflexes, discovered in distant postural muscles after a mechanical disturbance to the prime mover (Marsden, Merton and Morton, 1978). These reflexes compensate for body sway, but precede any mechanical disturbance to the postural muscles themselves. They appear to be centrally driven by afferent information from the disturbed limb as is the case for the indirect response in the flexor pollicis longus described here. However, when a flexion response was elicited by a pull to the waist or contralateral arm, it was not accompanied by any evidence of contraction of the proximal arm muscles, which are used to prevent the body from falling forward if the hand is holding on to a solid object. So the indirect response in the long thumb flexor while tracking is not part of a more widespread postural response. (In fact, in the circumstances of the experimental situation used here, it is the leg muscles which show appropriate distant anticipatory postural reflexes (Traub, Rothwell and Marsden, 1979).) Nor is the *indirect* response an attempt to maintain accurate tracking, for it occurs when the subject is merely asked to keep his thumb on the lever.

As it turned out, any wrist disturbance that displaced the thumb from its target caused a burst of activity in the thumb and finger flexors. Such a similar response to two opposite stimuli is characteristic of a startle reflex. However, it had none of the cardinal features of a startle response (Landis and Hunt, 1939); for example, activity was confined to flexor muscles of the forearm and did not habituate with repetition of the stimulus, which was itself highly specific. In any case, it did not occur when the arm was pulled with the tracking task held free in the hand.

Unlike the flexor grab response described here, the grasp reflex found in newborn infants or in patients with frontal lobe damage usually is driven by cutaneous stimuli to the palm of the hand or by local muscle stretch (Seyfarth and Denny-Brown, 1948). However, Adie and Critchley (1927) cite two cases in which pathological grasping was provoked by a stimulus to the contralateral hand, whilst in 'thalamic' monkeys with bilateral ablation of motor and pre-motor cortex, Bieber and Fulton (1938) have demonstrated flexion of the fingers in response to traction on the shoulder. Thus, we cannot state whether or not the flexor response that we have examined in normal man is related to a pathological or primitive grasp reflex.

The experiment with the sherry glass, however, shows that the response investigated in this study is a special form of grasp, perhaps best described as a grab reflex. A familiar situation to elicit it is on board a boat which rolls, when one instinctively grabs the glass (and the bottle) to stop it falling overboard. A pull to the wrist seems to evoke a similar response in our experiments causing a brisk thumb and finger flexion to hold on to a tracking task or to take hold of the sherry glass. This grab reflex is more powerful than local stretch reflexes, for it over-rides the direct effect of unloading the long thumb flexor.

SUMMARY

The effect of stretching or unloading flexor pollicis longus indirectly has been investigated by altering the force on the wrist while the subject tracked a moving spot on a cathode ray oscilloscope by flexing the top joint of the thumb against a fixed stiff lever. A radialward pull on the wrist, which lifted the thumb off the lever, thereby indirectly unloading flexor pollicis longus, caused a burst of EMG activity about 50 to 60 ms later, rather than the silent period seen at the same latency when the muscle was unloaded directly. A similar burst of activity occurred in the long finger flexors. Letting the wrist go, which caused the thumb to hit against the lever thereby indirectly stretching flexor pollicis longus, produced an initial burst of EMG activity about 50 ms later, as occurred when the thumb was stretched directly; but this was terminated prematurely after about 10 ms by a paradoxical silent period.

The response of flexor pollicis longus to indirect unloading was not altered by anæsthetizing the skin of the wrist under the chain pulling it, nor by anæsthesia of the thumb, so was not due to cutaneous stimuli. Nor was it affected by motor point anæsthesia of flexor pollicis longus, so it was unlikely to be due to changes in spindle input from that muscle. However, it was reduced considerably by bracing the arm, suggesting that it arose as a result of movement proximally at the shoulder. The response to indirect unloading of flexor pollicis longus by a pull on the wrist did not occur if the subject held the lever free in his hand, indicating that it was dependent on and adapted to the task. A similar response to a pull on the wrist occurred if the subject was asked merely to hold his thumb and fingers adjacent to a full sherry glass. In these circumstances wrist release also caused a thumb flexion.

Such an automatic flexion response or 'grab reflex' helps the subject to maintain contact of his digits with an object when his hand is displaced from it, provided that is his intent. Although the response occurs too early to be voluntary, it depends on the nature of the task and the subject's prior instruction.

ACKNOWLEDGEMENTS

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TRANSMISSION AND SCANNING ELECTRON MICROSCOPY OF SPONGIFORM CHANGE IN CREUTZFELDT-JAKOB DISEASE[1]

by S. M. CHOU, W. N. PAYNE, C. J. GIBBS, JR., *and* D. C. GAJDUSEK

(From the West Virginia University Medical Center, Morgantown, W. Va. and NINCDS, National Institutes of Health, Bethesda, Maryland)

INTRODUCTION

CREUTZFELDT-JAKOB disease (CJD) was once thought to be a rare form of dementia having only academic interest. This was drastically changed with the demonstration that the disease is histopathologically similar to kuru (Klatzo, Gajdusek, and Zigas, 1959; Chou and Martin, 1971) and also is transmissible to subhuman primates through the inoculation of extracts from biopsies or autopsies of brains from human cases of CJD (Gibbs, Gajdusek, Asher, Alpers, Beck, Daniel and Matthews, 1968). Because of the histopathological features, transmissibility and the nature of the infectious agent, CJD has been grouped with kuru, scrapie and transmissible mink encephalopathy (TEM), and designated as 'subacute spongiform virus encephalopathy' (Gibbs and Gajdusek, 1969, 1973); the dementia secondary to this encephalopathy is now referred to as 'transmissible virus dementia' (TVD) (Gajdusek and Gibbs, 1972). Recent reports that CJD has also apparently been transmitted from human to human through corneal transplantation (Duffy, Wolf, Collins, DeVoe, Streeten and Cowen (1974), from a formalin-fixed CJD brain (for eight months) to subhuman primate (Gajdusek, Gibbs, Collins and Traub, 1976), and also through the use of stereotactic electrodes (Bernoulli, Stegfried, Baumgartner, Regli, Rabinowicz, Gajdusek and Gibbs, 1977) have again focused our attention on the unique properties of the agent of CJD. The agent appears to be sensitive to chloroform, ether, various detergents and lipid solvents, yet resistant to proteases, nucleases and ultra-violet and ionizing radiation (Asher, Gibbs and Gajdusek, 1976). These properties are so atypical of most viruses that the term 'unconventional virus' was applied (Gajdusek, 1977); it appears to affect or associate with the lipid rich cell membranes of the host or perhaps is itself partially constituted by lipids (Bass, Hess and Pope, 1974). With the above points in mind we set out to scrutinize the vacuoles of spongiform change from cases of human and monkey CJD with respect to (1) the membrane structure of these vacuoles and (2) the presence of any particulate substance which might represent the infectious agent by correlating the findings of transmission (TEM) and scanning (SEM) electron microscopy.

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[1] Presented at the 52nd Annual Meeting of the American Association of Neuropathologists at San Francisco, California, June 1976.

MATERIALS AND METHODS

The present study includes 3 human cases of CJD with rather brief clinical courses of about two months, and 3 new world monkeys (1 capuchin and 2 spider) with relatively longer incubation periods than the average of sixteen to nineteen months. The clinical histories of the 3 human CJD cases are as follows:

Case 1 (A3631)

A 62-year-old male retired coal miner started to show a personality change, disorientation, ataxia, lethargy and dementia one and a half months prior to death. Physical examination on admission revealed an elderly demented person who laughed inappropriately. There were ill-defined myoclonic jerks and coarse intention tremors. Both upper and lower limbs showed cog-wheel type rigidity. EEGs showed markedly severe generalized abnormalities with slow and spike waves, predominantly over the left occipital region; pneumoencephalogram demonstrated signs of cortical atrophy and mild hydrocephalus. A biopsy was taken from the left occipital region (SP72-2714) and revealed changes typical of subacute spongiform encephalopathy. A portion of the specimen was immediately fixed for TEM and SEM. The patient went steadily downhill and died four weeks after admission.

Autopsy was limited to the brain and it revealed generalized cortical atrophy especially over the bifrontal and temporal regions. The brain weight was 1175 g. Cerebral arteries showed minimal arteriosclerosis. Symmetrical dilatation of the lateral ventricles and rounding of the lateral recesses were present. The lentiform nuclei appeared atrophic. Microscopically severe spongiform change was noted in sections from all cortical ribbons studied but most severely in the occipital cortex. The mid-zones of the cortical layers were preferentially involved. Astrocytosis varied from area to area, but it was most intense in the occipital cortex and minimal in the frontal cortex. The spongy degeneration and astrocytosis also involved the basal ganglia (the putamen more severely than the globus pallidus) and the tegmentum of both the midbrain and the pons. The medulla and spinal cord were free of spongiform change.

Case 2 (A3991)

A 61-year-old white male developed restlessness, unstable gait, mild jerking movements, and insomnia two months prior to death. Physical examination on admission revealed a relatively alert and occasionally confused person with bilateral spasticity, hyperreflexia, ataxic gait and bilateral nystagmus. His mental function progressively deteriorated during the hospitalization; and he showed marked bilateral cerebellar signs, frontal lobe dysfunction, widespread myoclonic jerks and profound dementia. He became completely mute and unresponsive; death occurred one month after admission. Pneumoencephalogram showed slight ventricular dilatation and evidence of cortical atrophy.

Brain weight was 1400 g. Marked congestion of leptomeningeal veins, apparently secondary to bilateral pulmonary œdema, resulted in a mild degree of brain œdema. The lateral ventricles were not dilated, and there was no gross cortical atrophy except over the parietal region. Microscopic examination of the parietal, occipital, frontal and temporal cortices revealed generalized spongiform change in the corresponding order of severity. Patchy areas of neuronal loss accompanied the spongiform change. Astrocytosis was seen in the parieto-occipital cortex; however, it was not always accompanied by status spongiosus. The changes were, in general, more severe in the right cerebral hemisphere. Similar changes were seen in the basal ganglia. In the cerebellum, spongiform change was confined to the molecular layer and astrocytosis to the granular cell layer and the white matter.

Case 3 (A79-183)

A 71-year-old man exhibited subtle personality changes for seven months prior to death. Shortly before death he exhibited myoclonic jerks and severe generalized weakness. Physical examination showed suck, snout and grasp reflexes. There was also increased muscle tone bilaterally. EEG showed triphasic pattern compatible with CJD.

Brain weight was 1100 g. There was generalized atrophy of the cerebrum; the occipital area was most prominently affected. There was mild dilatation of the lateral ventricles. There was no neuronal cell loss or spongiform change in the spinal cord. Marked spongiform change was noted in the caudate nucleus and in the frontal cortex; astrocytosis was minimal. The parietal lobe demonstrated only minimal spongiform change in the depths of sulci. Examination of the temporal cortex showed rare senile plaques in the hippocampus which were also seen rarely in the frontal cortex. There were no neurofibrillar tangles or granulovacuolar degeneration. The occipital cortex was severely involved with spongiform change but again with only minimal astrocytosis. No kuru plaques were seen in the cerebellum.

Four control cases were also examined from other patients with neurological illnesses (Cases 4, 5, 6 and 7). No spongiform change was seen in any of these patients.

Case 4 (465)

A 58-year-old woman with a three-year history of dementia. Brain biopsy showed neurofibrillary tangles and senile plaques; a diagnosis of Alzheimer's disease was made.

Case 5 (524)

A 65-year-old woman with a brain biopsy demonstrating findings consistent with Alzheimer's disease.

Case 6 (A75-33)

A 66-year-old man who experienced a cardiac arrest and subsequently developed an encephalopathy.

Case 7 (A75-82)

A 40-year-old woman who was demented. Biopsy and autopsy findings indicated a diagnosis of neoplastic angioendotheliosis.

The clinical history of three monkeys with CJD is as follows:

Case 361

This male adult capuchin monkey developed fine tremors in the limbs and body thirty-five months after intracerebral and intravenous inoculation with 10 per cent suspension of brain homogenate from a CJD chimpanzee (A-82). His gait had become stiff-legged, and movements were often awkward and gave a hopping appearance. Two months after onset, he began throwing out his right leg while running. He became moderately ataxic and myoclonic jerks appeared. He became progressively ataxic, inactive and lethargic eight months after the onset and was killed by intracardiac perfusion with a combined formalin-glutaraldehyde fixative, under anæsthesia, according to the two-step perfusion method described by Peters (1970).

Case 294

This spider monkey was inoculated with 10 per cent brain suspension (0.1 ml i.v. and 0.1 ml i.c.) from a human CJD case twenty-six months before the onset of tremors and ataxia. Ataxia progressively worsened over the course of one and a half months and was accompanied by marked myoclonic jerks and lethargy. He was killed by perfusion under anæsthesia exactly twenty-eight months after the inoculation (about two months after the onset of clinical symptoms).

Case S-325

Another spider monkey was inoculated with 10 per cent brain suspension (0.2 ml i.c. and 0.1 ml i.m.) from a human case of CJD. Symptoms similar to those occurring in Case 294 developed twenty-four months after inoculation. The animal was killed by perfusion under anæsthesia two and a half months after the onset of these symptoms.

Case 419

For control, a well perfused and fixed CNS from an adult male capuchin monkey that had never been previously used for any inoculation study was examined.

Both the biopsy and autopsy specimens, along with control human and monkey specimens prefixed in glutaraldehyde, were post-osmicated for both TEM and SEM. For SEM the fixed specimens were dehydrated through gradients of ethanol and specimens placed in a paraform-cylinder with 100 per cent ethanol; these were cryofractured under liquid nitrogen according to Humphreys, Spurlock and Johnson (1974). The specimens were then critical-point dried in the Polaron E-3000 apparatus and coated with gold in Argon gas with the ISI sputter-coater (Model PE-5000) after which they were affixed to a stub with the fractured surfaces upwards. The specimens were examined at 15 kV in an ISI MINI-SEM; images were recorded on Polaroid 52 film. For TEM the osmicated specimens were dehydrated in graded ethanols and embedded in Araldite-Epon mixture after they were bathed in propylene oxide. Some specimens which were viewed initially in the SEM were placed in several changes of fresh propylene oxide and then transferred to Araldite-Epon mixture and embedded as usual for TEM (Humphreys *et. al.*, 1975). One micron semi-thin sections stained with Paragon were studied before the blocks were trimmed down for ultra-thin sections. Some of the specimens were embedded without osmication. Ultra-thin sections with or without uranyl acetate lead citrate staining were studied with an AEI (Corinth 275) electron microscope.

RESULTS

Light Microscopy

Areas of spongiform change and neuronal cell loss were found in the cortical grey and basal ganglia from all human animal cases of CJD studied. We follow Masters and Richardson (1978) in defining spongiform change as the presence of small vacuoles within the neuropil; whereas status spongiosus is defined as marked gliosis and cavitation in the neuropil. Astrocytosis was much less prominent and was often not even observed in the areas of spongiform change. The majority of vacuoles were in the neuropil and were only occasionally found in neuronal perikarya. Semi-thin resin sections from control monkey tissue demonstrated only round and hollow structures which correspond to perfused and emptied capillaries; whereas vacuoles of spongiform change are characterized by the presence of fragmented membranes within the vacuoles (figs. 1A, C). Human and monkey vacuoles of spongiform change appeared morphologically identical and were widely variable in size. They often fused with one another; membranous fragments were constantly seen within the vacuoles (figs. 1A, C). No kuru plaque was found in any of the human or monkey specimens, nor was there any congophilic angiopathy.

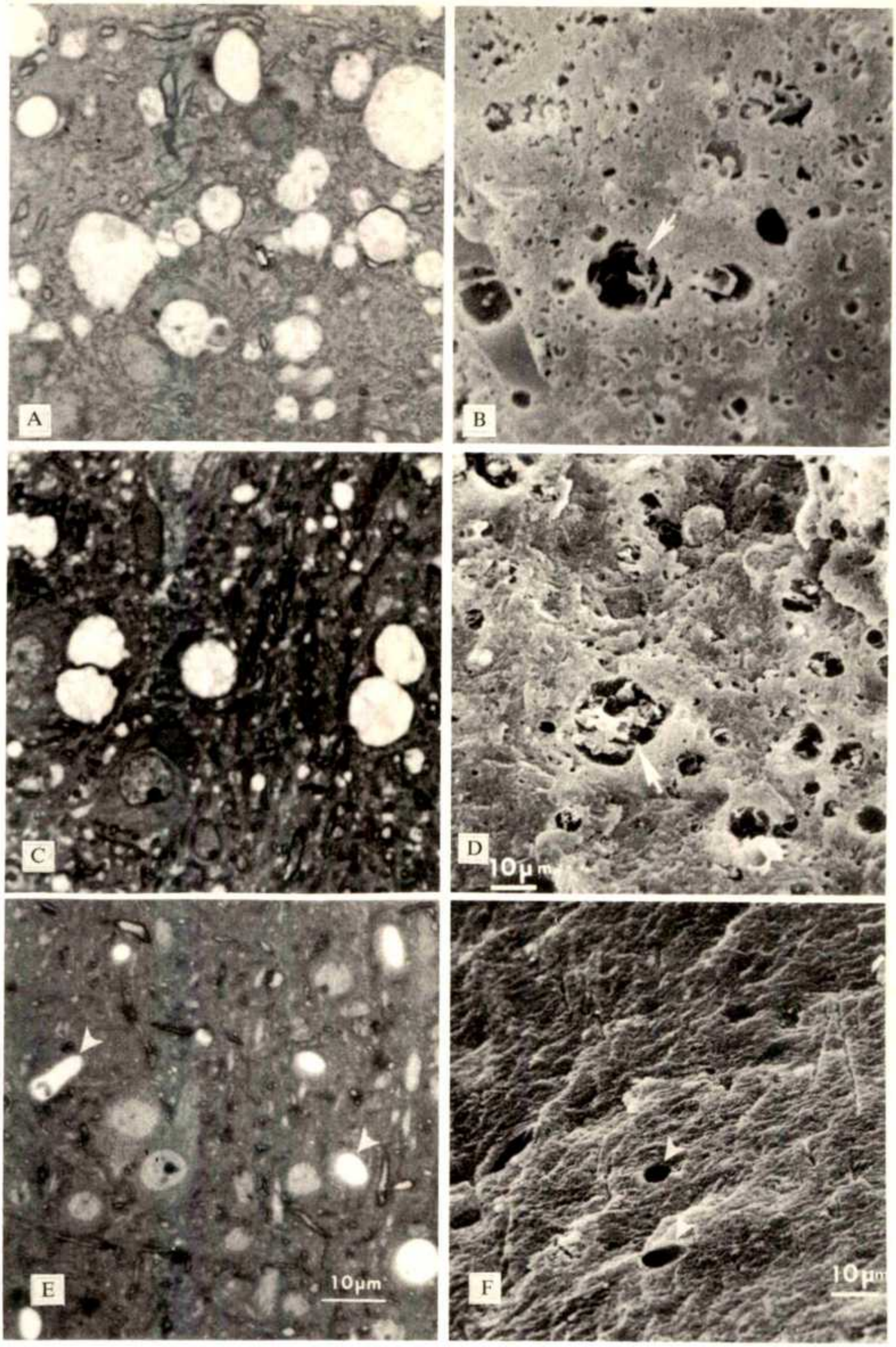

FIG. 1. Human with Creutzfeldt-Jakob disease (*Case 3*) showing vacuoles present in A, one micron paragon-stained section and B, freeze fractured tissue examined under SEM where arrow indicates large vacuole. Monkey with transmitted Creutzfeldt-Jakob disease (*Case 294*) showing vacuoles in C, one micron section and D, freeze fractured brain tissue (arrow again indicates large vacuole). E, control human (*Case 7*) and F, monkey (*Case 419*) tissue demonstrating no vacuoles; arrow heads indicate perfused and emptied capillaries. A, C, E, one micron resin-embedded sections. B, D, F, freeze-fractured tissue.

Scanning and Transmission Electron Microscopy

Human and monkey vacuoles were indistinguishable on both TEM and SEM even though monkey tissue had been perfused and the human tissue was formalin or glutaraldehyde prefixed. On SEM, control and diseased tissues were as easily differentiable as on light microscopy (figs. 1B, D, F). In addition, TEM results were identical on sections stained with lead citrate and uranyl acetate and on unstained sections.

The major findings concerned (1) membrane alterations and (2) particulate structures present on intravacuolar membranes. We note that no structures resembling conventional viruses were seen on either TEM or SEM.

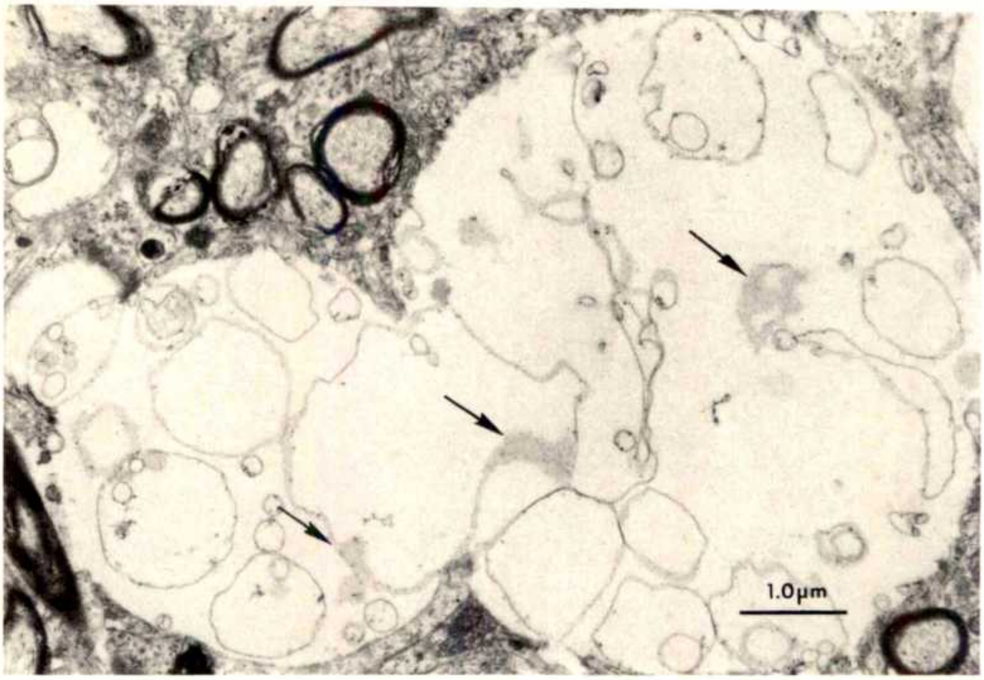

FIG. 2. Two coalesced vacuoles from human Creutzfeldt-Jakob disease (*Case 1*). Arrows indicate amorphous membranes with associated electron-dense particles. Areas of membrane splitting are also apparent. Uranyl acetate-lead citrate staining under TEM.

Often vacuoles coalesced and formed larger vacuoles (fig. 2). Intravacuolar membrane alterations (fig. 2) were of two types: (1) splitting of the unit membrane into its two electron dense sub-units and (2) formation of puffy amorphous membranes. These two findings were often noted within the same vacuole (fig. 3). The splitting of a unit membrane into its two layers on TEM correlates well with the ulcerated or defective membrane areas seen on SEM (fig. 4) which may represent loss of a layer of the unit membrane. The rough elevated areas seen on other SEM specimens (fig. 5) correspond to areas seen on TEM as focally thickened and amorphous membranes (figs. 2 and 3). These TEM findings are considered to represent altered and focally thickened subunit membranes rather than unit membranes cut tangentially. Vacuoles with anomalous intravacuolar membranes were sometimes seen in the perineuronal region in both TEM (fig. 6) and SEM (fig. 7).

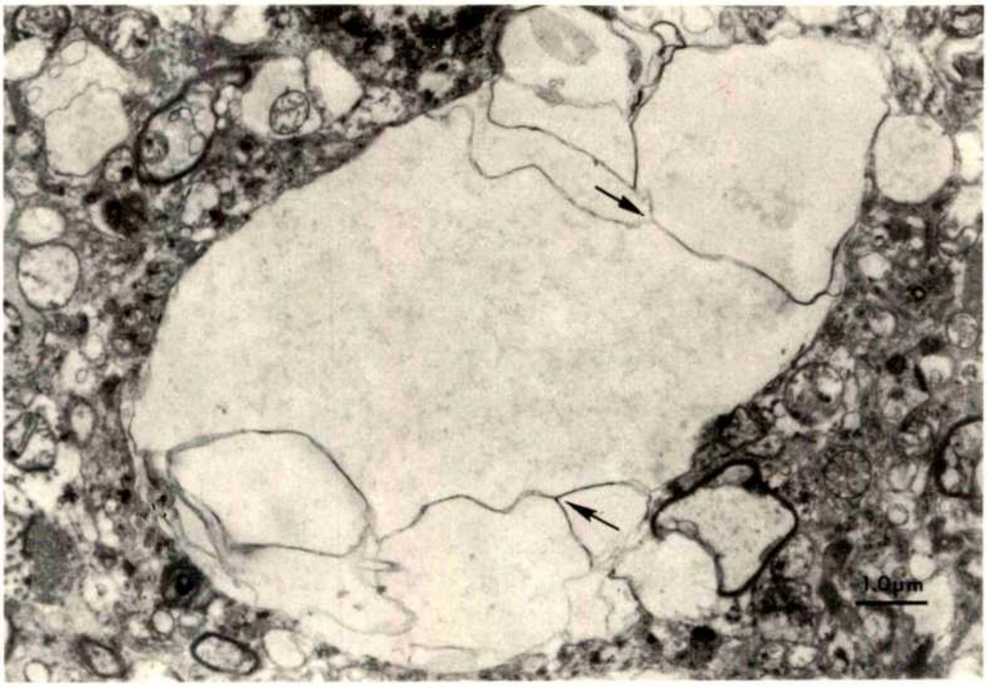

FIG. 3. Human vacuole (*Case 3*) (uranyl acetate-lead citrate staining) demonstrating membrane fragments within the vacuole and amorphous membranes with associated particles; arrows indicate membrane splitting. (TEM.)

The undulating character of focally thickened membranes was frequently associated with small blisters of variegated shapes and sizes within vacuoles examined with SEM (fig. 8); these are seen to correspond to intravacuolar vesicles seen on TEM which appeared to be swollen vesicles, perhaps synaptic, enlarging to become blisters (fig. 9).

Focally thickened membranes seen on TEM sometimes exhibit 10 nm electron-dense particles which are not seen elsewhere in the tissue (figs. 2, 3, 6 and 9). These particles sometimes form aggregates. They often occur in areas where the thickened amorphous membranes are undulating and thus might be related to irregular

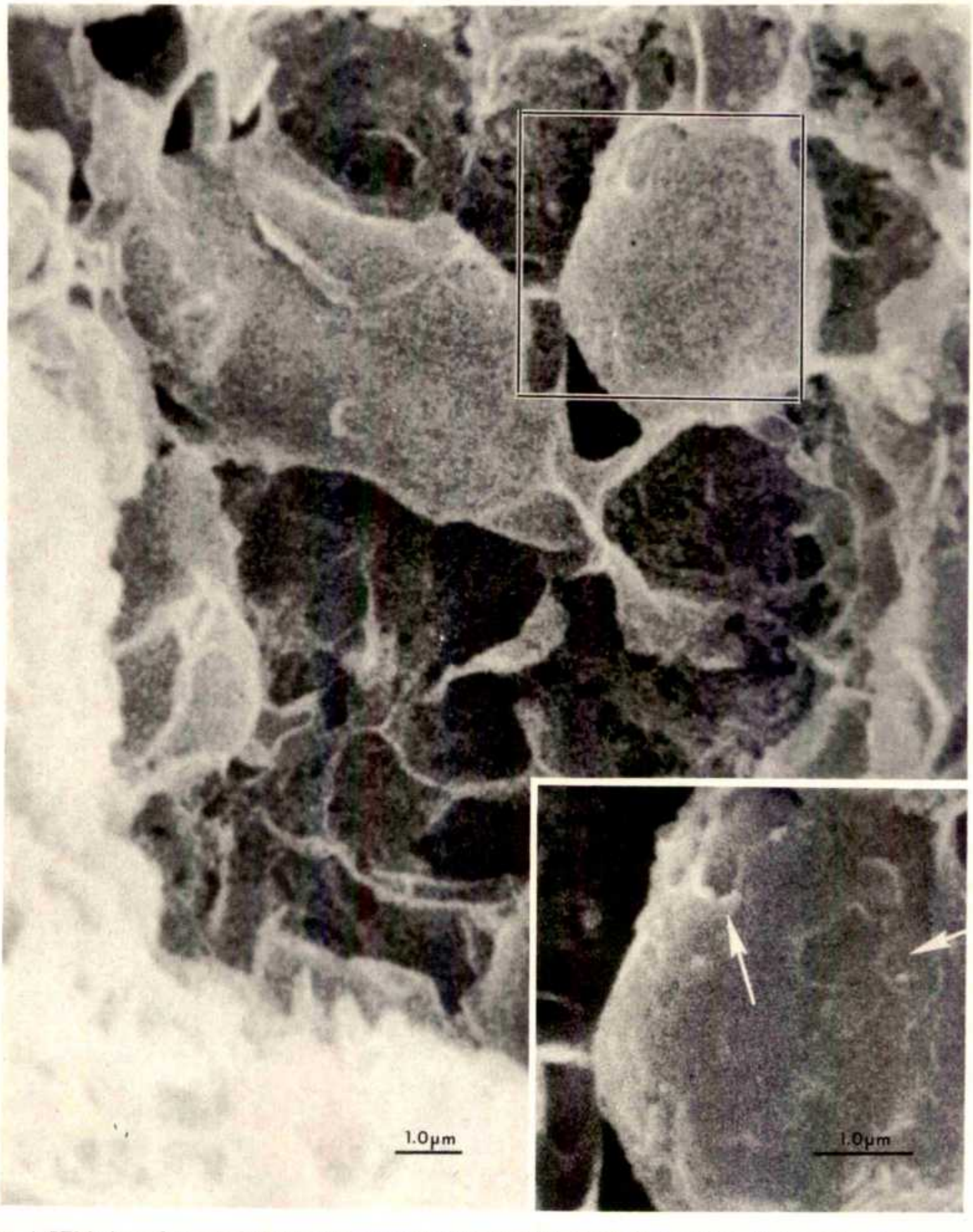

FIG. 4. SEM view of a vacuole from a human case of Creutzfeldt-Jakob disease (*Case 2*) shows the entire blister; whereas inset demonstrates ulcerated areas of its membranes (arrows).

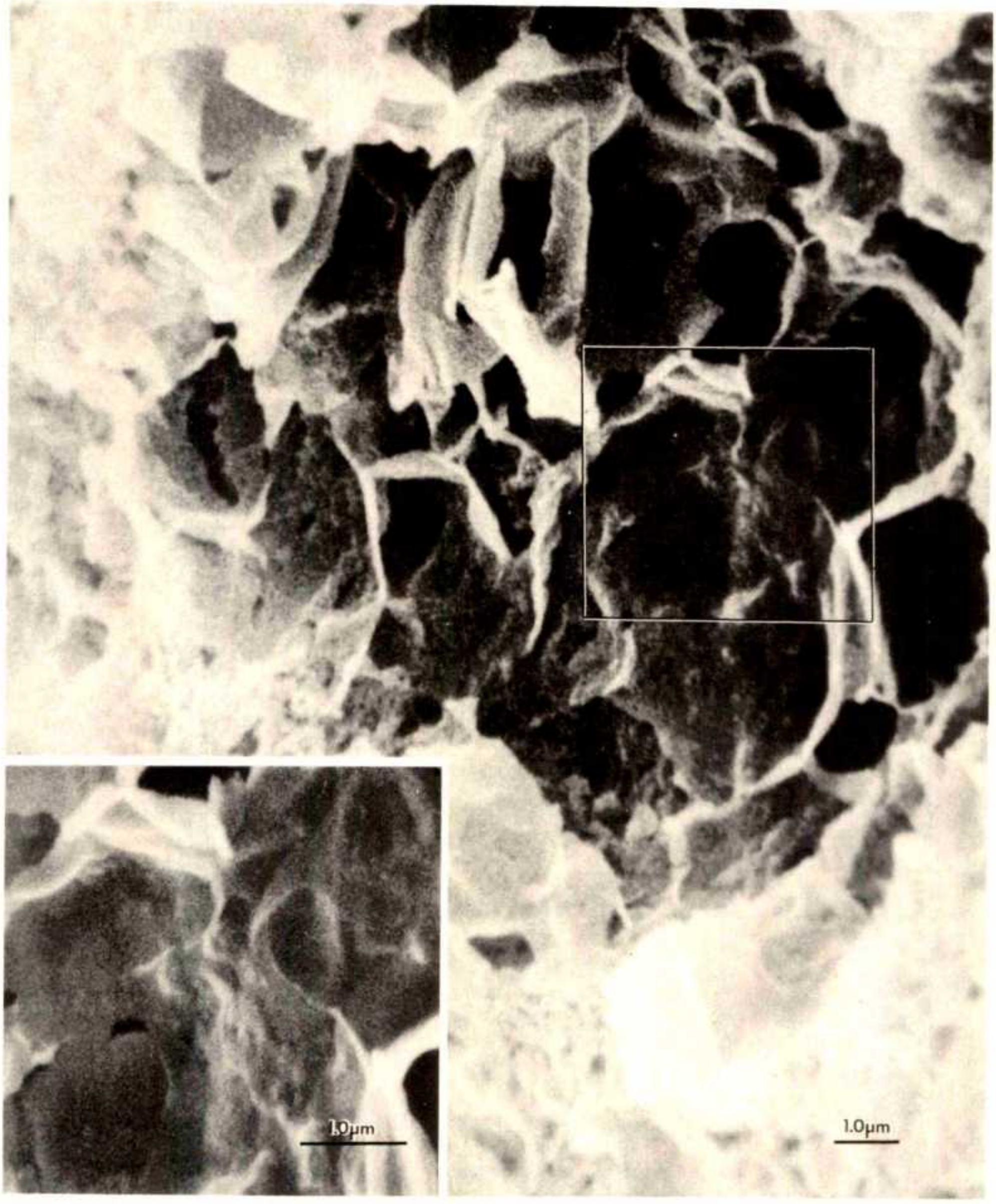

FIG. 5. SEM view of another human Creutzfeldt-Jakob disease vacuole (*Case 2*) which shows thickened amorphous membranes best seen in the inset.

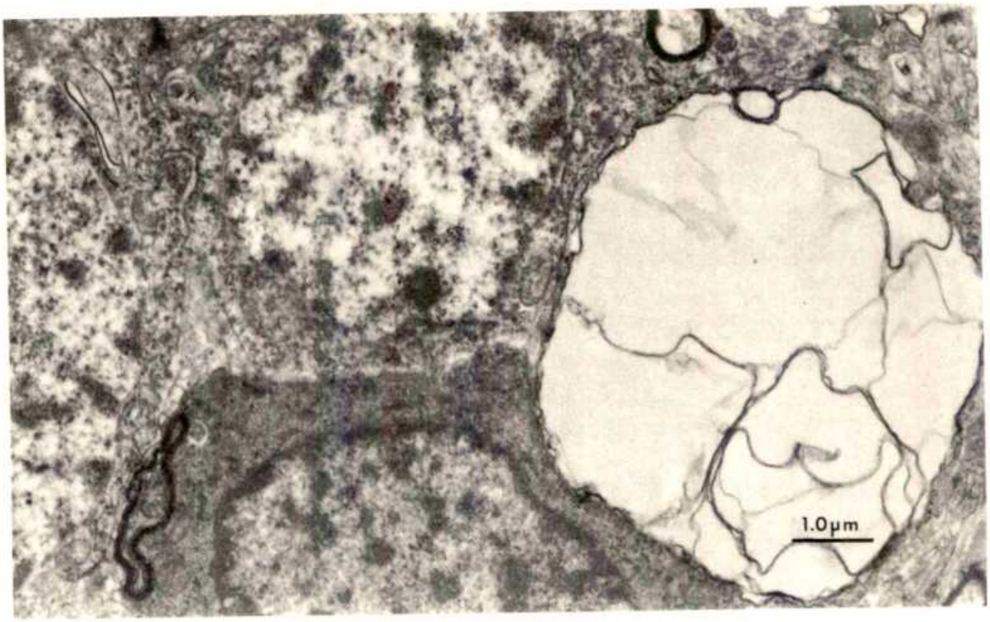

FIG. 6. Vacuole near the cell nucleus as seen in TEM. Monkey (*Case 294*).

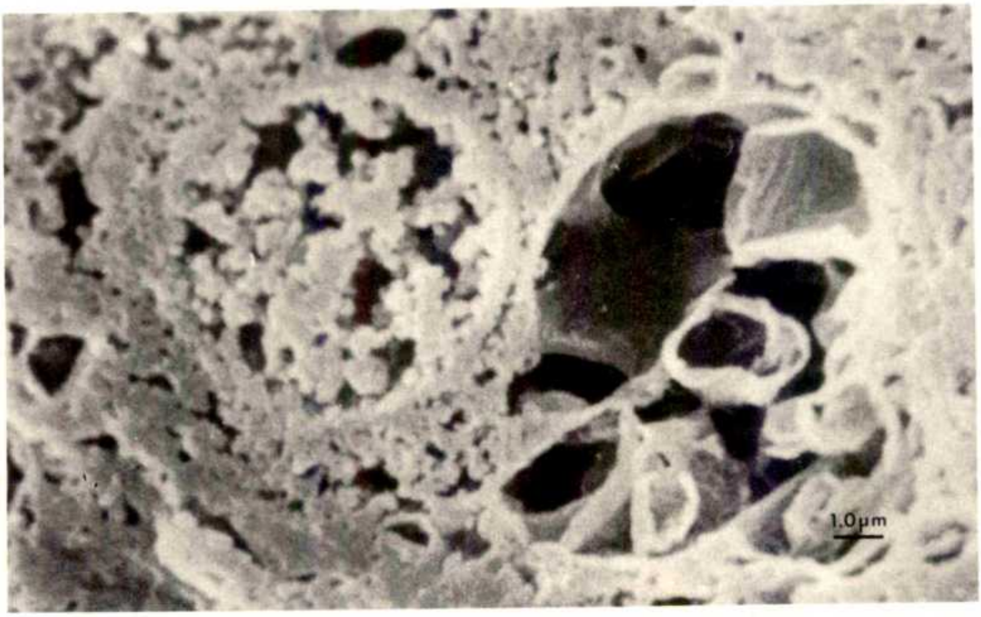

FIG. 7. Vacuole near the cell nucleus as seen in SEM. Human (*Case 3*).

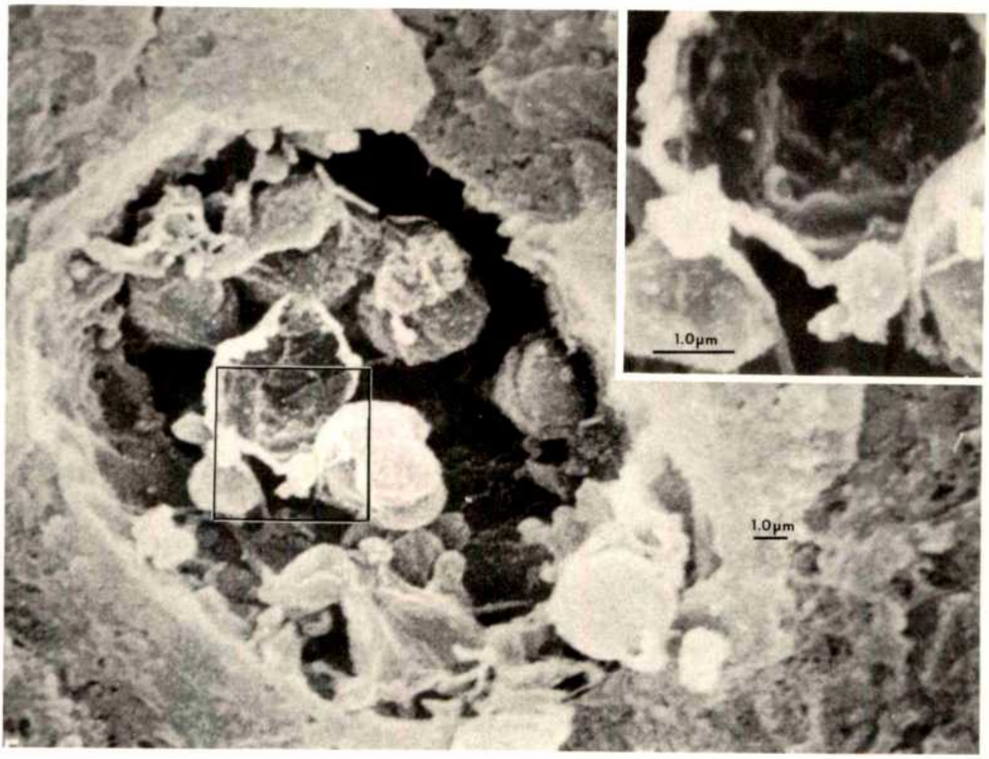

FIG. 8. SEM view of a large vacuole in a monkey (*Case 294*) having transmitted Creutzfeldt-Jakob disease. Note that one blister in the vacuole appears to have been fractured open. *Inset* shows irregular small particulate structures or possible tiny blebs 70 to 150 nm in diameter.

particulate structures (70 to 150 um) seen on SEM (figs. 8 and 10). These SEM findings were never noted on any surrounding structures and are thus not derived from the gold coating procedure. That the 10 nm particles seen on TEM are not artefacts of uranyl acetate-lead citrate staining is attested by their being present identically in osmium post-fixed sections both with (figs. 2, 3, 6 and 9) and without (fig. 11) this staining. Sections were also taken for TEM from tissue which was glutaraldehyde-fixed without post-osmication in an attempt to further ascertain the origin of these particles, but the contrast of the non-osmicated and unstained or stained tissue was too poor to clearly demonstrate these 10 nm particles.

TEM was also performed on tissue used previously for SEM. Comparison of this tissue with previous photomicrographs reveal a quite similar appearance of the spongiform change except for the presence of the gold coating on the fractured surfaces and the exposed membrane surfaces within the vacuoles. No drying artefact was observed.

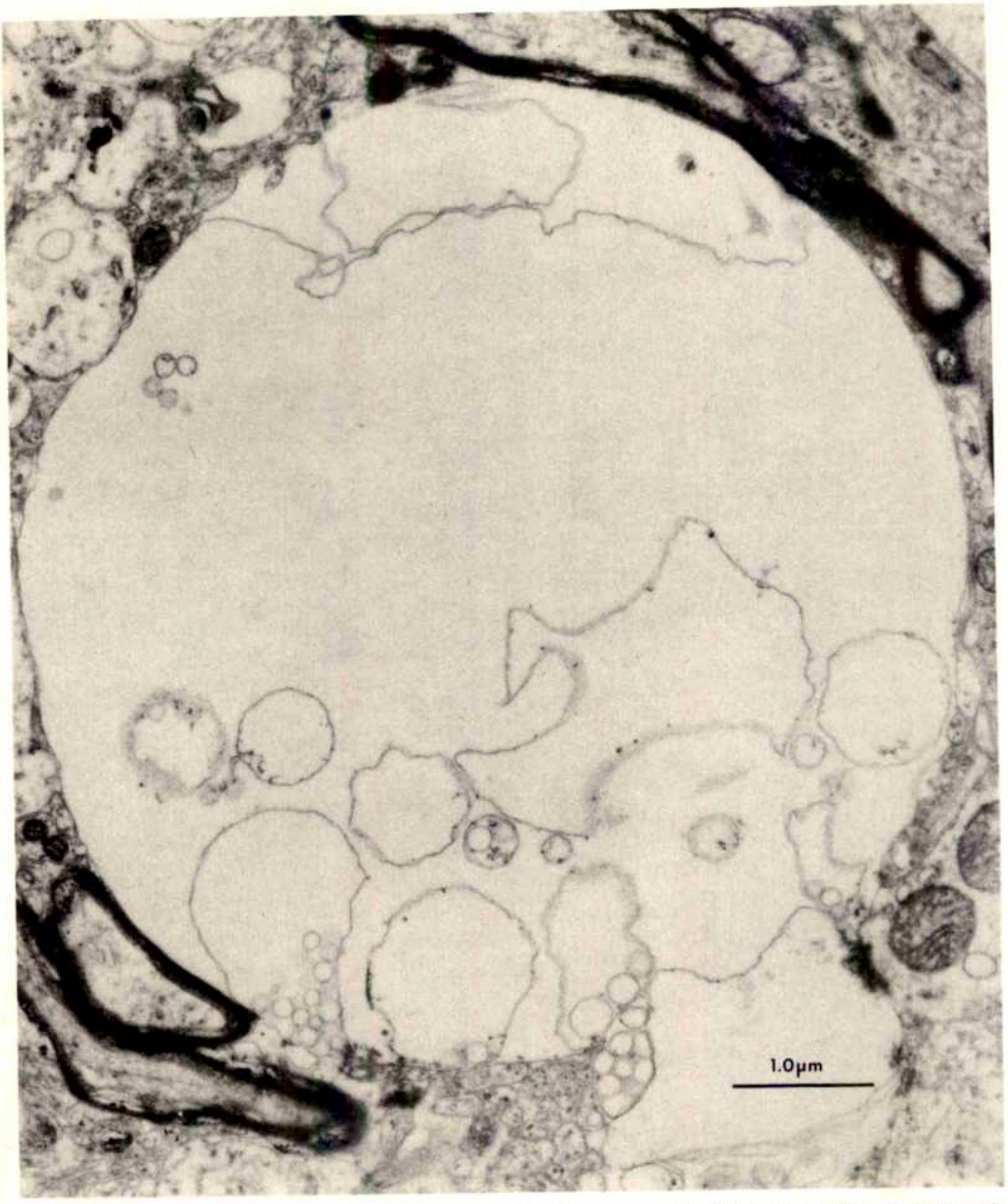

FIG. 9. Human Creutzfeldt-Jakob disease (*Case 1*) showing apparent budding of membranes of vacuoles. Amorphous membranes are again present with electron-dense particles. Uranyl acetate-lead citrate staining under TEM.

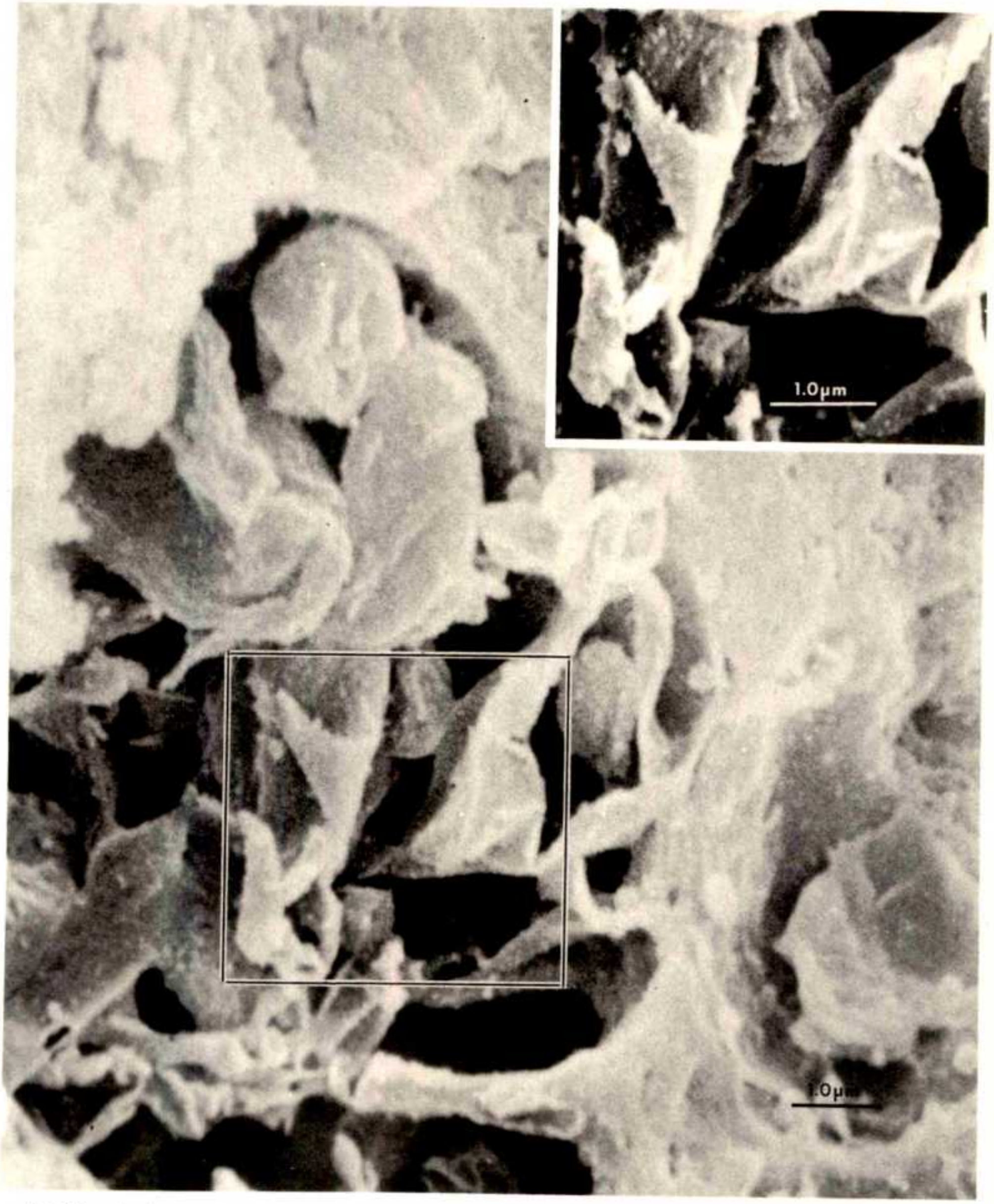

FIG. 10. Vacuole from a monkey with Creutzfeldt-Jakob disease (*Case 294*). *Inset* again reveals 70 to 150 nm structures seen in fig. 8. (SEM.)

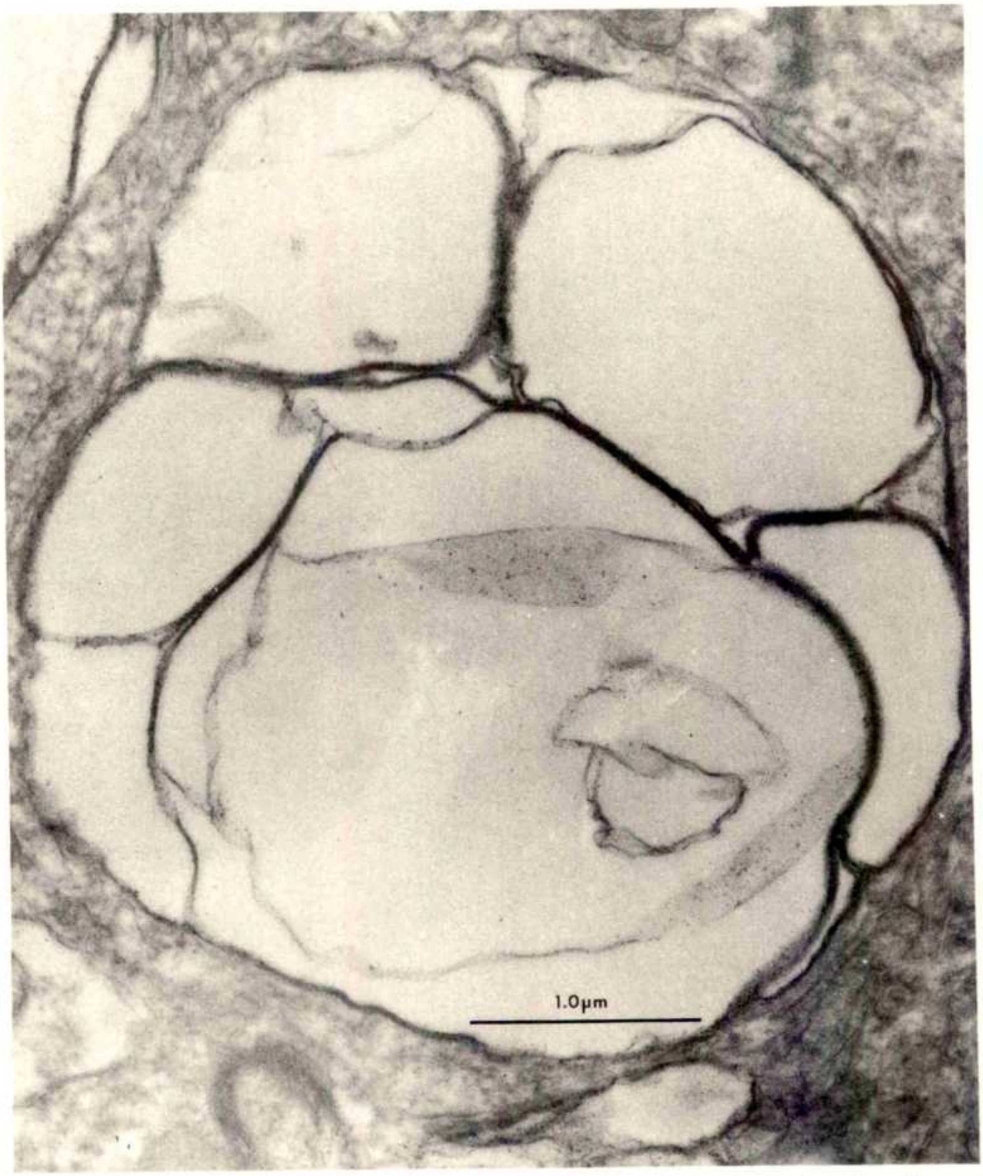

FIG. 11. Monkey having transmitted Creutzfeldt-Jakob disease (*Case 294*). Unstained sections from the vacuole again demonstrate 10 nm particles. (TEM.)

DISCUSSION

Our results indicate that spongiform change is the most characteristic and crucial lesion in Creutzfeldt-Jakob disease; astrocytosis appears to be a rather limited and secondary phenomenon. One has to be careful in evaluating the morphology of spongiform change since it may simply arise as an artefact of poor fixation. We discount this possibility in our material for two reasons:

1. spongiform change appeared in all human cases and monkey transmissions of Creutzfeldt-Jakob disease and in none of the controls;
2. the perfusion method used with the monkeys has been shown to provide excellent fixation.

We are in complete agreement with Masters and Richardson (1978) and Masters, Kakulas, Alpers, Gajdusek and Gibbs (1976) that spongiform change is pathognomic for Creutzfeldt-Jakob disease and that status spongiosus may arise late in the course of prolonged cases as a non-specific finding accompanying gliosis. To their characterization of spongiform change as the presence of small vacuoles of various sizes within the neuropil, the qualification should be added that these vacuoles must also be membrane-bound and may often have membraneous fragments or blisters within them; the vacuoles of status spongiosus caused by glial scarring are not membrane-bound and membranous fragments are absent within. The membrane-bound nature of the vacuoles of spongiform change in Creutzfeldt-Jakob disease is well seen in both ultrathin TEM sections and paragon-stained thick sections, since membranous lipids are better preserved in the resin-embedded than the paraffin-embedded tissue. In the latter the distinction between vacuoles of spongiform change and those of status spongiosus is understandably blurred because of poor preservation of membranes both along and within the vacuoles.

Light and electron microscopic features of spongiform change in both original human and transmitted (primary and secondary passage) Creutzfeldt-Jakob disease appear identical (Beck, Daniel, Matthews, Stevens, Alpers, Asher, Gajdusek and Gibbs, 1969). This fact, along with the clinical similarities of monkey to human Creutzfeldt-Jakob disease, suggests that this animal model is indeed a valid means of studying this disease. Morphological study is more rewarding in animal tissue since the use of perfusion methods allows one to obtain better fixed tissue and thus to be more confident in drawing conclusions.

The major findings of the present work centre on two areas: alterations of membranes and the presence of particles on these altered membranes. Strong evidence of altered membranes was obtained by both TEM and SEM. TEM revealed splitting of unit membranes into single component leaflets and showed further that these single leaflets were often puffy, amorphous and focally thickened; these findings are quite compatible with the SEM evidence (1) of erosion or ulceration of a layer of membrane and (2) of other focally thickened areas of membranes. TEM studies by Lampert, Gajdusek and Gibbs (1972, 1975) on CJD and experimental scrapie have also revealed areas of focally thickened amorphous membranes as well as areas of proliferating curled membranes; those authors suggested that the primary site of damage in both diseases is in membranes. In addition, apparent splitting of unit membranes has been noted on photomicrographs from the brain of a patient presumably having Creutzfeldt-Jakob disease (Martin and Vial, 1964). Alvira, Mendoza and Mandybur (1976) have recently concluded on high resolution TEM that the curled membranes in vacuoles of Creutzfeldt-Jakob disease are half the width of the trilaminar unit membrane structure.

SEM revealed the presence of particulate structures of variable size (70 to 150 nm) on membranes within vacuoles. These particles may well represent gold-coated aggregates of fine electron-dense particles accentuated by undulations and irregularities in the focally thickened membrane seen on TEM. These focally thickened membranes often exhibit 10 nm electron-dense particles on TEM which may be implicated as an ultrastructural correlate for infectious agent of Creutzfeldt-Jakob disease. Others have not remarked on these particles which were presumably dismissed as artefacts of uranyl acetate-lead citrate staining. This possibility is eliminated by their presence on photomicrographs from unstained sections. One intriguing question is whether these particles bear any relation to the characteristic sub-unit periodicity of 10 to 12 nm in diameter in membranes within vacuoles in two human cases of Creutzfeldt-Jakob disease as reported by Alvira *et al.* (1976) who suggested that particles of nucleic acid might be present in such membranes. Osmium is known to stain unsaturated lipids in cell membranes, and Nielson and Griffith (1979) have recently produced evidence suggesting that osmium may also have a role in linking proteins and unsaturated lipids. To these must be added a third property of osmium, namely, the ability to combine with nucleotides (Cole, Wiggins and Beer, 1977; Chang, Beer and Marzilli, 1977). The possibility thus arises that some component, probably lipid or nucleic acid but conceivably protein, of the infectious agent is being seen on our sections. It is also conceivable that the 10 nm particles might represent calcium salt deposits secondary to a membrane altering action of the infectious agent. Engel (1977) cited evidence to support the idea of membrane defects in Duchenne muscular dystrophy allowing an influx of calcium into the cell to cause damage to it. It is possible that membrane alterations caused by the infectious agent might alter permeability to calcium or other ions and thus bring about high concentrations of calcium in the altered membrane systems of vacuoles. In this case, the 10 nm particles would be a purely secondary phenomenon.

Other evidence also exists for a role of membrane alterations in Creutzfeldt-Jakob disease and scrapie. Dubois-Dalcq, Rodriguez, Reese, Gibbs and Gajdusek (1977) found a decrease in the number of normally occurring intramembrane particles in membranes of vacuoles and in blebs within vacuoles in both scrapie and Creutzfeldt-Jakob disease. As they noted, however, this is not only seen in scrapie and Creutzfeldt-Jakob disease, but also occurs in myelin sheaths when hexachlorophene is given. Yu and Manuelidis (1978) also raised the question of membrane alterations from the point of view of ganglioside changes occurring in the brain which cannot be explained simply by neuronal loss or astrocytosis; they proposed that the infectious agent alters ganglioside metabolism and thus the structure of membranes. Alternatively, one might suppose that the infectious agent alters membranes more directly by incorporating itself into them and replicating in them. As we discuss below, the infectious agent certainly seems intimately involved with membranes.

If Creutzfeldt-Jakob disease is a primary disease of membranes, as has been suggested, a limited pathogenic mechanism can be proposed. Focally thickened membranes may have altered permeability leading to changes in electrolyte balance and osmolarity which could cause increasing accumulations of fluid and certain electrolytes within vacuoles and thus lead to eventual disruption of membranes. We observed both swollen synaptic vesicles and vacuoles consisting primarily of swollen dendrites. These pre- and post-synaptic changes may account for the markedly abnormal EEGs in Creutzfeldt-Jakob disease as hypothesized by Bignami and Forno (1970).

The question which remains concerns the nature of the infectious agent. The physical characteristic of this agent and its resistance to formalin and heat have been well described by Asher *et al.* (1976). The hypothesis has been presented that it might be a self-replicating membrane fragment (Gibbons and Hunter, 1967) or a membrane fragment to which a small piece of RNA is attached (Asher *et al.*, 1976). The supposition that an infectious agent consisting wholly or partly of a membrane fragment would produce spongiform change in a wide variety of host cell membranes seems quite reasonable. Large (70 to 150 nm) particulate structures associated with anomalous membranes seen in SEM may be related to smaller particles (10 nm) seen in TEM and may represent the membrane-altering action of this infectious agent; more study is necessary to further elucidate these structures and to evaluate infectivity associated with them. We also note that viroids, as recently reviewed by Diener (1979) are excellent candidates in many ways to be the causative agent of Creutzfeldt-Jakob disease. Even here, though, there are some problems: for example, viroids are associated with the nucleus while the agent for Creutzfeldt-Jakob disease appears to predominantly involve the cytoplasm. Viroids are also more resistant to lipolytic compounds than is the agent for Creutzfeldt-Jakob disease. We feel that the idea of a small piece of nucleic acid bound to a small membrane fragment is a promising way of viewing the CJD agent; the present results are quite compatible with such a concept.

SUMMARY

Brains from three human cases of Creutzfeldt-Jakob disease and three monkey cases of transmitted Creutzfeldt-Jakob disease were examined. Spongiform change was present in all cases on both light and electron microscopic examination. Electron microscopic examination revealed membrane alterations within vacuoles in all cases. On SEM, both ulcerated and focally thickened membranes were apparent; TEM revealed splitting of unit membranes as well as focally thickened

amorphous membranes. Small blisters with 70 to 150 nm particulates were seen on membranes in SEM. TEM revealed 10 nm electron-dense particles which might be either part of the infectious agent or a membrane alteration caused by it. The significance of these findings was discussed.

ACKNOWLEDGEMENTS

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HUMAN VISUAL RESPONSES IN THE ABSENCE OF THE GENICULO-CALCARINE PROJECTION

by J. L. BARBUR, K. H. RUDDOCK *and* VICKI A. WATERFIELD

(*From the Departments of Physics (Biophysics) and Zoology, Imperial College, London SW7 2BZ*)

INTRODUCTION

In primates, retinal nerve fibres project to the dorsal lateral geniculate nucleus, which in turn projects to the striate cortex. There is also a projection to the superior colliculus of the midbrain and from there, *via* the pulvinar, to a large and still undetermined area of the non-striate cortex. The 20 per cent or so of optic nerve fibres which project to the midbrain control the pupil reflex and visually controlled eye movements. In addition, there is a projection, known as the accessory optic system, which appears to be involved in basic visual light-dark differentiation (Pasik and Pasik, 1971). It has been established that the visual field is mapped topographically on to the superficial (upper) layers of the superior colliculus (Schiller and Koerner, 1971; Goldberg and Wurtz, 1972), although some single neurons in these layers have large receptive fields, thus for these the mapping is essentially coarse. The collicular projection appears to derive primarily from Y-type ganglion cells (de Monasterio, 1978; Weller, Kaas and Wetzel, 1979), which respond selectively to transient stimuli and, correspondingly, collicular units are responsive to flashed and to fast-moving targets (Goldberg and Wurz, 1972).

The visual performance of animals from which the striate cortex is ablated suggests that there are two principal pathways involved in visual function, the collicular pathway, which mediates visual spatial localization, and the geniculo-cortical pathway, which provides fine discrimination of stimulus parameters (Sprague, 1966; Trevarthen, 1968; Schneider, 1969). Considerable recovery of visual function, including pattern recognition, follows removal of monkey striate cortex (Weiskrantz, 1972), although damage to both the striate cortex and posterior cortical regions results in more permanent loss of function (Pasik and Pasik, 1971). Visually controlled eye movements can be performed by animals lacking either the superior colliculus or the striate cortex, but they are significantly impaired if corresponding projection areas are removed (Mohler and Wurtz, 1977). The view that visual spatial orientation and visual pattern recognition arise in separate neural pathways is, therefore, a simplification.

Localized damage to the human visual cortex causes permanent scotoma in the corresponding visual field position (Holmes, 1918; Teuber, Battersby and Bender, 1960), and Brindley, Gautier-Smith and Lewin (1969) describe two subjects with extensive damage to the visual cortex, whose sole visual discrimination was between the onset of general illumination and darkness. Riddoch (1917) found that in some cases of visual scotoma caused by cortical lesions, responses to flashed or moving targets were selectively spared and, more recently, several groups of investigators have described visual functions arising in the 'blind' hemifields of hemianopic subjects (Pöppel, Held and Frost, 1973; Weiskrantz, Warrington, Sanders and Marshall, 1974; Perenin and Jeannerod, 1978). The subject studied by Weiskrantz and co-workers was able to discriminate pattern orientation and spatial distribution of targets presented within the 'blind' hemifield, and there was some indication of colour discrimination.

We report the results of a study on a subject with a hemianopic visual field caused by accidental damage to the left hemisphere and/or the optic radiation. It is shown that this subject, G., can detect flashed and moving targets located within the 'blind' hemifield and the parametric characteristics of these responses are described and analysed. No non-visual cortical function appears to have been impaired by the accident.

SUBJECT

G., a 22-year-old male, was involved in a road accident when 8 years old, as a result of which the left hemisphere was damaged and he became 'blind' in the right half-field. Ophthalmic investigations, carried out immediately after the accident, revealed an almost complete right homonymous hemianopia which, on retesting some fourteen months later, was found to be virtually unchanged (T. D. H. Gray; private communication). Subsequent to the accident, he has been unable to detect or recognize objects located in the 'blind' hemifield and he regards himself as blind in the right half-field. For some three months following the accident, he suffered a severe squint which was corrected by 'patching' treatment. We have examined visual responses in G.'s normal left half-field and found that the following functions are similar to those of subjects with normal vision: rod and cone threshold illumination levels, foveal colour matches, the contrast threshold elevation effect (Blakemore and Campbell, 1969) and its binocular inhibition (Ruddock and Wigley, 1976), and fine stereoscopic discrimination. G. cannot identify the 3-D image structure of random dot stereograms (Julesz, 1971), which implies lack of global stereoscopy. Details of G.'s responses to binocular stimulation have been given elsewhere (Ruddock, Waterfield and Wigley, 1979).

METHODS

The experiments were designed to determine G.'s responses to flashed and moving targets presented to his right, 'blind', hemifield. Preliminary experiments established that he is capable of detecting such stimuli and we therefore constructed a four-channel Maxwellian system, using high quality 135 mm and 50 mm multi-element lenses (Takumar), which provided targets moving with constant velocity, through a fixed displacement angle, at a chosen location in the visual field. The four beams were derived from a single quartz-halogen-tungsten source, and produced the following stimuli: beam 1, the test target, which could be presented moving at a constant velocity in the range 0.1 to 100 deg/s, or as a flash of selected duration; beam 2, fixation targets; beam 3, a 17.5 degrees circular background field across the centre of which the target moved, and beam 4, a 48 degrees circular background field. The beams were projected through an effective exit pupil of diameter 1.5 mm. The location of the target relative to the fixation points was monitored by a grey code detector and infra-red switches, which permitted stimulus positioning, accurate to 0.3 degrees. The test pattern transparencies were produced photographically on high contrast (Kodalith) film, and the retinal illumination levels of all four beams were controlled, stepwise, by mechanical insertion of neutral density filters. In addition, continuous control of the test and 17.5 degrees background field illumination levels was provided by motor-driven neutral density wedges. The transmission characteristics of the wedges were calibrated *in situ* and their driving motors were controlled by the subject. Electromagnetic (Vickers Instruments) shutters and interference filters (Balzers B40, with half-band width ±5 nm) controlled, respectively, the presentation duration and wavelength of the different stimuli. Except in measurements of spectral sensitivity functions, white light (colour temperature $\simeq$ 3,000 degrees K) stimuli were used in the present investigation. All stimulus parameters, such as target velocity, retinal location and the variable in most experiments, retinal illumination level, were automatically sampled and recorded on paper-tape each time a measurement was made. An eight-channel processor, designed for this purpose, has been described elsewhere (Barbur and Nunn, 1978). Illumination levels were calibrated with a Macam Instruments Radiometer.

Where appropriate, functions measured for G.'s 'blind' hemifield were also measured for a subject with normal vision. Ideally, comparison data should have been obtained for G.'s normal hemifield, but this was not possible because of the restricted time available for experimentation on G. As monocular vision in G.'s normal hemifield is similar to that of normal subjects in all functions examined, we consider that data for other, normal, subjects provide a valid basis for comparison. Three subjects with normal vision, V.W., a 23-year-old female, I.H., a 23-year-old male, and J.B., a 26-year-old male, took part in the investigation.

Except in experiments concerned with target location, G. was instructed to respond to stimuli only if he experienced a visual sensation. It was established that a flashed or moving target presented to G.'s 'blind' hemifield elicits a visual sensation and he was, therefore, able to establish threshold illumination levels, etc., for such targets. Data for target location (fig. 3) refer, however, to targets presented at illumination levels below that required for visual detection, thus G. was forced to respond to an 'unseen' target. Forced response methods for testing hemianopes have been employed more generally in other studies (*see* particularly Weiskrantz *et al.*, 1974) and differences between some of the results presented here and those obtained in other studies may reflect differences in response criteria. Eye movements were monitored visually by the experimenter and, in later experiments, by an infra-red corneal reflection device with a reading accuracy of 30′ arc. Both monitoring methods established that G.'s detection of the targets in the 'blind' hemifield was not accompanied by eye movements of significant amplitude.

RESULTS

Visual Field Maps

Visual field maps were determined by measurement of the threshold illumination level for detection of a 1.2 degrees diameter circular target presented against a 48 degrees diameter circular background field of illumination level 2.1 log trolands. Target locations within the 48 degrees background field were selected in random order and the subject was instructed to fixate voluntarily on a central 0.4 degrees diameter spot. The subject achieved a threshold setting by reduction of the target illumination level until the target was just no longer detectable. Location was defined relative to the fixation point and was changed by slow movement of the target across the field to the required position. Values of log threshold illumination level, log I_t, obtained for G., are plotted in fig. 1A, and there is a sharp change in log I_t at the vertical meridian. Log I_t equal to 4.5 log trolands denotes the maximum available illumination level and, at this setting, G. was unable to detect targets presented to the blind hemifield, except for a region of some 3 to 4 degrees around the fovea. Foveal sparing is not uncommon in hemianopia (*see* Teuber *et al.*, 1960)

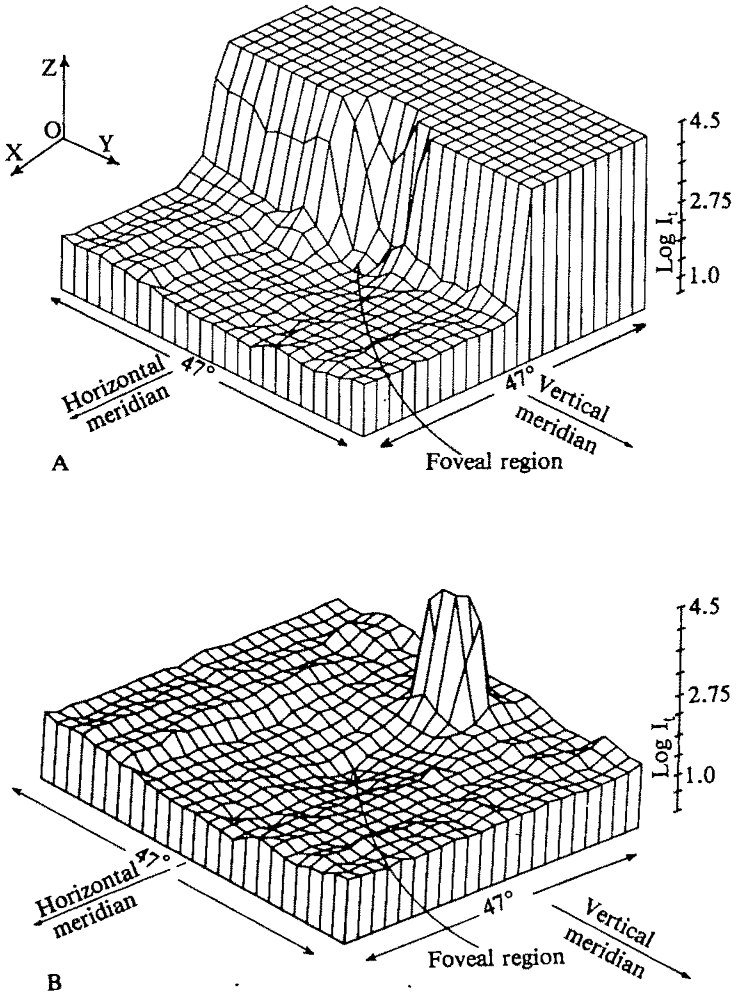


FIG. 1. A, *Subject G.* Log threshold illumination level, log I_t, for detection of a 1.2 degrees diameter circular target, presented in stationary mode, at discrete positions on a uniform 48 degrees diameter background field of illumination level 2.2 log trolands. The plateau to the right of the vertical meridian corresponds to the maximum illumination level available in the test channel, for which the subject was unable to detect the presence of the stationary target. B, *Subject J.B.* Log threshold illumination level, log I_t, for detection of a 1.2 degrees diameter circular target presented for 250 ms at discrete locations on a uniform, 48 degrees diameter background field of illumination level 2.2 log trolands.

and although eye movements could cause spread of sensitivity into the blind hemifield, there is a sharp change in sensitivity at non-foveal points on the vertical meridian. Further, G. is aware of visual sensitivity extending into his 'blind' hemifield whilst he fixates on a small central target. Sensitivity measurements were also made with the target presented in a 250 ms flash, and it was found that in this case, G. could detect it at locations up to 10 degrees into the 'blind' hemifield. On increasing the target diameter from 1.2 to 5 degrees, G. could detect the flashed target at any location in the blind hemifield. This is illustrated by fig. 2 in which the threshold illumination level for detection of a 10.5 × 2.3 degrees rectangular target is plotted against its location on the horizontal meridian. In this experiment, the target was spatially structured, consisting of randomly distributed geometric shapes, such as triangles and circles, of typical dimension 1 degree, seen by normal subjects as black against a white background. It is apparent that G. detects the flashed target at all retinal locations, but when it is not flashed, he is unable to detect it outside the central 4 degrees of the 'blind' hemifield, even if it is slowly translated over the stationary rectangular window (fig. 2). Comparison data for normal vision (subject J.B.) are plotted in fig. 1B, and the notable feature is the increase in log I_t around the blind spot. We note that the blind spot was not revealed in measurements on G. because of the relatively large targets used and/or because the scan across the horizontal meridian (fig. 2) failed to traverse the blind spot to a significant extent.

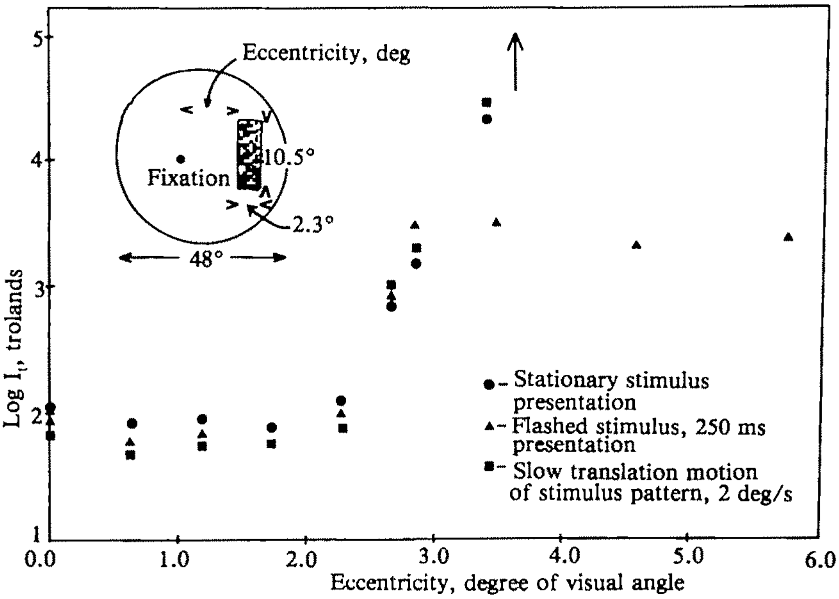


FIG. 2. *Subject G.* (blind hemifield). Log threshold illumination level, log I_t, for detection of a spatially structured target, plotted against target eccentricity, measured in degrees of visual angle from the fixation point, along the horizontal meridian. ● = target presented in the stationary mode. ▲ = stimulus flashed for 250 ms once every two seconds. ■ = target structure moved continuously over the stationary rectangular window at a speed of 2 deg/s. Each data point is the mean of 5 or 6 readings, with typical standard error 0.03 log units.

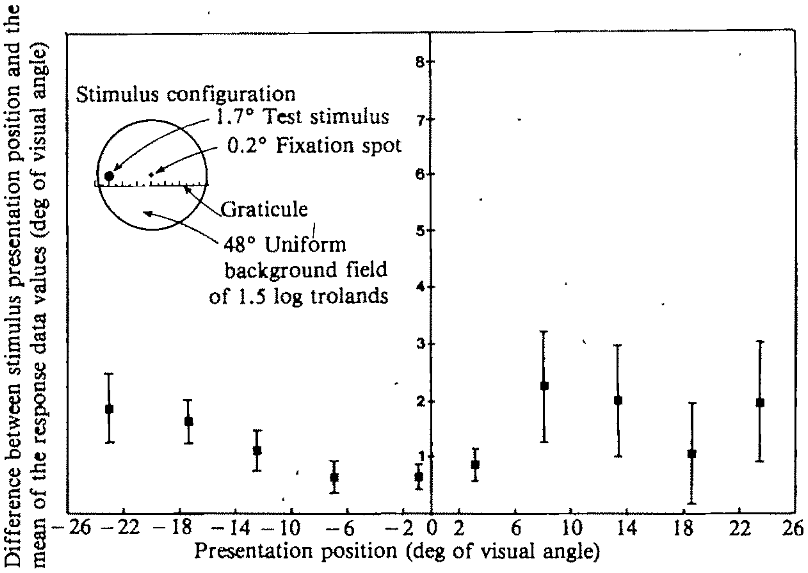


FIG. 3. *Subject G*. The mean error in locating the position of the flashed stimulus plotted against stimulus eccentricity. Each point represents the average of 12 measurements and the error bars indicate the SD associated with each set of data. Positive abscissal values refer to the 'blind' hemifield.

Subjectively, G. reports that a flashed target of near-threshold illumination level appears as 'a dark shadow', located in the 'blind' hemifield. At higher illumination levels, it sometimes appears as a localized, bright flash. In a later section, we will examine critically the possible contributions of scattered light to G.'s detection of the flashed target, but as a preliminary indication that detection is localized to the 'blind' hemifield, we tested semi-quantitatively his ability to locate targets in the visual field. A calibrated graticule was placed along the horizontal meridian of the 48 degrees background field, and the subject was requested to state verbally the calibration number of the apparent graticule scale position of a flashed, 1.7 degrees diameter circular test target. The target was presented at different retinal locations, taken in random order, and twelve measurements were made at each location. The results, expressed as the difference between the mean estimated and the actual stimulus location plotted against the actual location, are shown in fig. 3, and although the error bars for the 'blind' hemifield are larger than for the normal hemifield, the two sets of mean values are similar. The illumination level of the target was some 0.5 log units below the threshold for G.'s 'blind' hemifield, but the results show that he could identify its position in his 'blind' hemifield. This report is consistent with previous reports about 'blind' field function in hemianopic subjects (Pöppel *et al.*, 1973: Weiskrantz *et al.*, 1974; Perenin and Jeannerod, 1978).

Detection of Moving Targets

The minimum velocity at which a moving target of fixed illumination level can be detected was determined as a function of retinal location in G.'s 'blind' hemifield. The subject was instructed to increase the velocity of the 3.6 degrees diameter circular target from zero until it could just be detected and the direction of movement identified. The target movement was directed along the horizontal meridian, with alternate scans in opposite directions, and no attempt was made to distinguish between detection thresholds for movement towards and those for movement away from the vertical meridian. Measurements were made for three target illumination levels, I_t, and in each case the 48 degrees background field illumination level was 1.4 log trolands. The three values of I_t were: that required for detection of the target when presented as a 250 ms flash; 1.5 log units greater and 0.3 log units less than this value. These illumination levels are different for each retinal location and in the experiment, appropriate adjustments were made for each stimulus presentation. The experimental data are plotted in fig. 4, and show that, at the lowest of the three illumination levels, G. can detect the target only for locations $>$ 17 degrees from the fixation point and for speeds above some 50 deg/s. Increase in illumination level enables G. to detect the target at all retinal locations and at lower velocities. G. could readily identify the direction of target movement, except when it was at near-threshold velocity and illumination level.

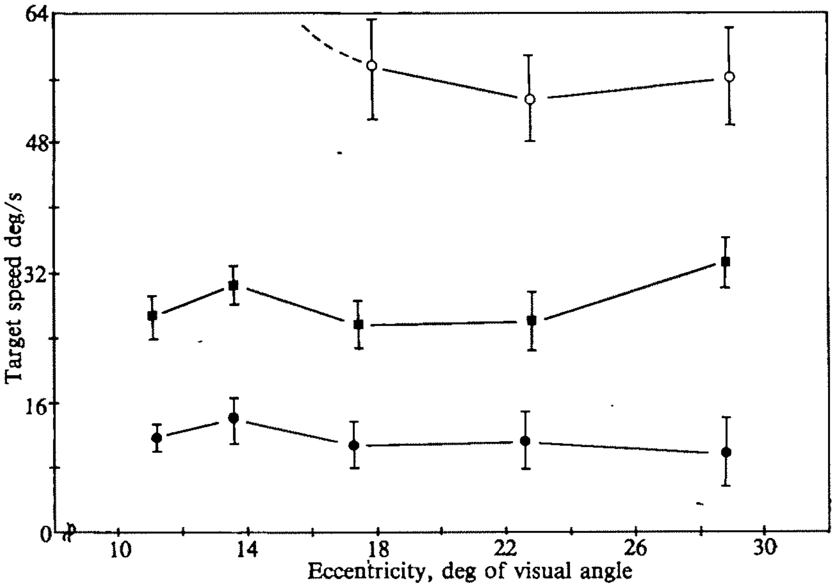


FIG. 4. *Subject G. (blind hemifield).* The minimum speed required for detection of a 3.6 degrees diameter circular test target, presented against a 1.4 log troland uniform background field, is plotted against stimulus location along the horizontal meridian. Each point represents the mean of 4 to 6 readings, and error bars represent the SDs. ■ = test target presented at the threshold illumination level required for its detection when presented at the appropriate eccentricity as a 250 ms stationary flash; ● = illumination 0.3 log units below and ○ = 1.5 log units above these values.

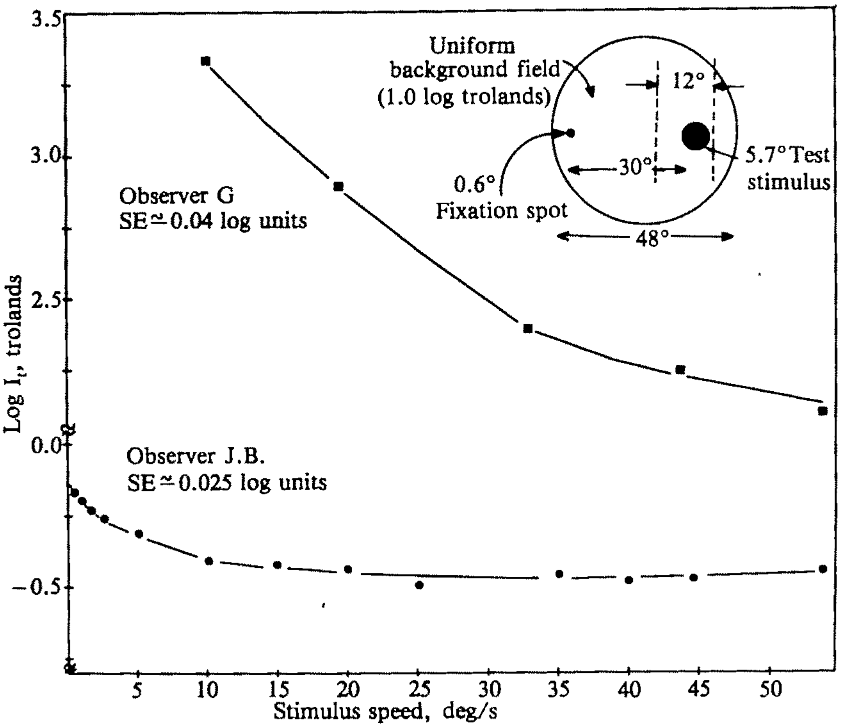


FIG. 5. Log threshold illumination level, log I_t, for detection of a 5.7 degrees diameter circular target, plotted against target speed, measured for the hemianopic subject's 'blind' hemifield (■) and for the normal subject J.B. (●). The stimulus was presented moving along the horizontal meridian through 12 degrees of visual angle centred 30 degrees off axis, with a uniform 48 degrees diameter white light background of illumination level 1.0 log troland. Each point is the mean of 4 to 6 readings, with typical standard errors of 0.04 log units (G.) and 0.025 log units (J.B.).

Threshold retinal illumination levels for detection were measured as a function of target speed for a 5.7 degrees diameter circular target moving through a visual angle of 12 degrees along the horizontal meridian. Stimuli were located 30 degrees off-axis, in G.'s blind hemifield, and the experimental values are plotted in fig. 5 together with comparison data for a normal subject, J.B. The results show that G. detects faster moving targets at lower illumination level than slower targets, and that minimum detectable velocity decreases as the target illumination level increases, in confirmation of fig. 4. In contrast to G.'s results, target illumination level has relatively little influence on the minimum velocity detected by the normal subject, J.B., whose threshold levels are some 2 log units lower than G.'s.

Detection of apparent movement was investigated with two 6 × 0.15 degrees bar-shaped stimuli, orientated with their long edges parallel and displaced laterally from each other by 3 degrees. Observations were made for G.'s blind hemifield, at retinal locations between 10 and 40 degrees along the horizontal meridian, with the two bar-shaped stimuli orientated either vertically or horizontally. The illumination level of each bar was set at 0.75 log units above threshold level for its detection when presented in a 50 ms duration flash. The two bars were presented sequentially, each for 50 ms, with a 50 ms delay between the cessation of the first flash and the onset of the second. Under these conditions, subjects with normal vision perceive a strong impression of movement in the direction from the first to the second flash. The sequence in which the two bars were presented, and their orientation (vertical or horizontal), were changed randomly from presentation to presentation. On every presentation, G. identified the direction of apparent movement as that which would be perceived by normal subjects, reporting that a 'dark shadow' traversed the visual field in the appropriate direction. We note that the 'movement' associated with our stimulus configuration is equivalent to a 3-degrees sweep (the separation of the two bars) in 50 ms, giving a velocity of some 60 deg/s, that is, in the high speed range to which G. is particularly sensitive (fig. 5).

Increment Thresholds for Detection of Flashed and Moving Targets

Threshold illumination levels, I_t, for detection of flashes and moving targets, were measured as a function of background field illumination level, I_B. Two background field configurations were employed: one was a 17.5 degrees diameter circle of illumination level I_B, surrounded by a larger, 48 degrees background field of illumination level 0.01 I_B, and the second was a 48 degrees circular field, of illumination level I_B. The target was a 5.7 degrees circular disc, which was presented either in stationary mode, for 250 ms every 2.5 s, or moving at constant velocity (40.0 deg/s) along the horizontal meridian. Threshold values obtained for G.'s blind hemifield (30 degrees off-axis on the horizontal meridian) are plotted in fig. 6A. Comparison data for G.'s normal hemifield (30 degrees off-axis, on the horizontal meridian) were measured for the stationary flashed target and are plotted, together with those for the normal subject, V.W., in fig. 6C. The relationship between I_t and I_B is similar for all four sets of data, but values for G.'s blind hemifield are some two log units greater than those for normal vision. Data obtained with the full 48 degrees background field are plotted in fig. 6B, and the results are very similar to those for the smaller background field, except that there is an increase of some 0.5 log units in the values of I_t. This difference will be examined further in the Discussion section dealing with possible effects of scattered light. Overall, the data of fig. 6 show that the same increment threshold mechanism operates in normal and 'blind' hemifield vision, but the latter requires a much greater (100 times) signal level for detection.

Increment Threshold Illumination Level as a Function of Target Area

Threshold levels were determined for stationary flashed circular targets, with diameters in the range 1.1 to 13.9 degrees (subject G.) and 0.48 to 24 degrees (subject J.B.) superimposed on a uniform 48 degrees background field of 0.5 log troland illumination level. The target, presented for 250 ms once every 3 s, was located 30 degrees off-axis in the 'blind' hemifield, and G. was instructed to reduce the illumination level of the target until it could just no longer be detected. The values are plotted in fig. 7, together with comparison data for a normal subject, J.B., measured both for 0.5 log troland and for zero background illuminations. The significant feature of G.'s data is the linear relationship between the threshold values, log I, and log A, with least squares slope −0.93, thus following Ricco's law over the full range of stimulus size investigated. J.B.'s results give variable slope for the 0.5 log troland background field and a least squares slope of −0.59 for zero background field. These results imply extensive linear summation in G.'s threshold responses, extending to illumination levels up to 4 log units above the normal dark threshold level. The data for the normal subject with a dark background field give a slope of −0.59, in approximate agreement with Piéron's law.

Spectral Sensitivity for Threshold Detection of a Moving Target

Spectral sensitivity functions were measured for detection of a 5.7 degrees diameter circular target, moving at 40.0 deg/s along the horizontal meridian. The monochromatic target moved through 12 degrees of arc, with the direction of motion reversed on alternate sweeps, against a uniform 48 degrees background field,

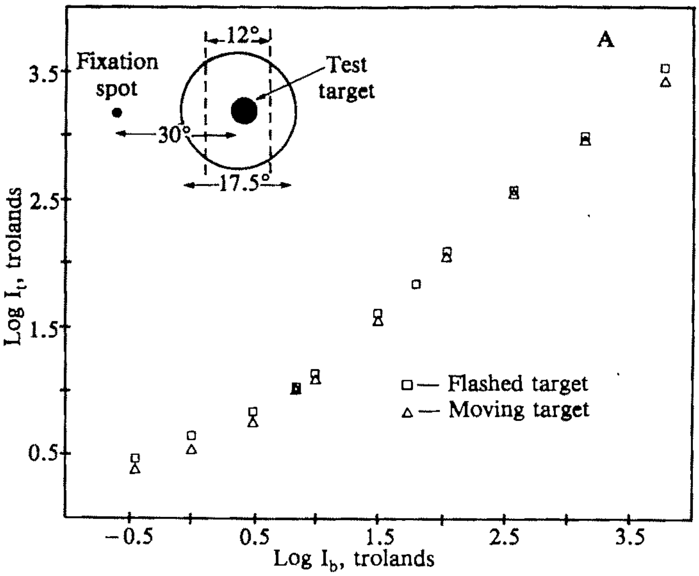
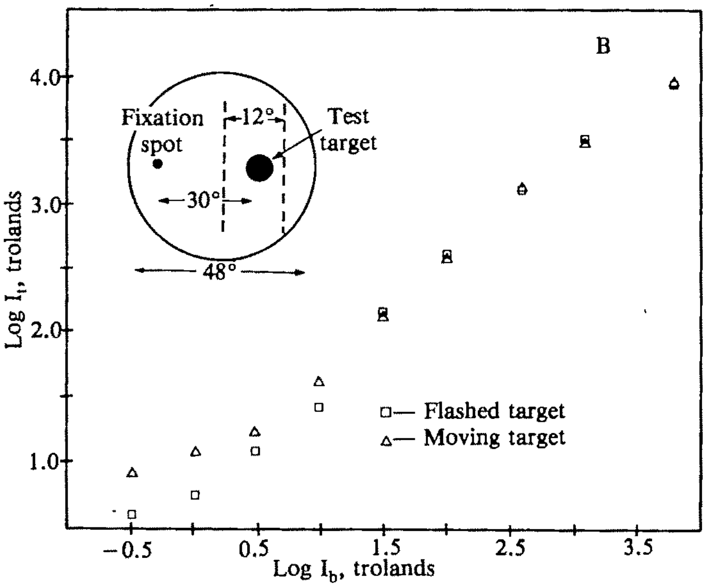
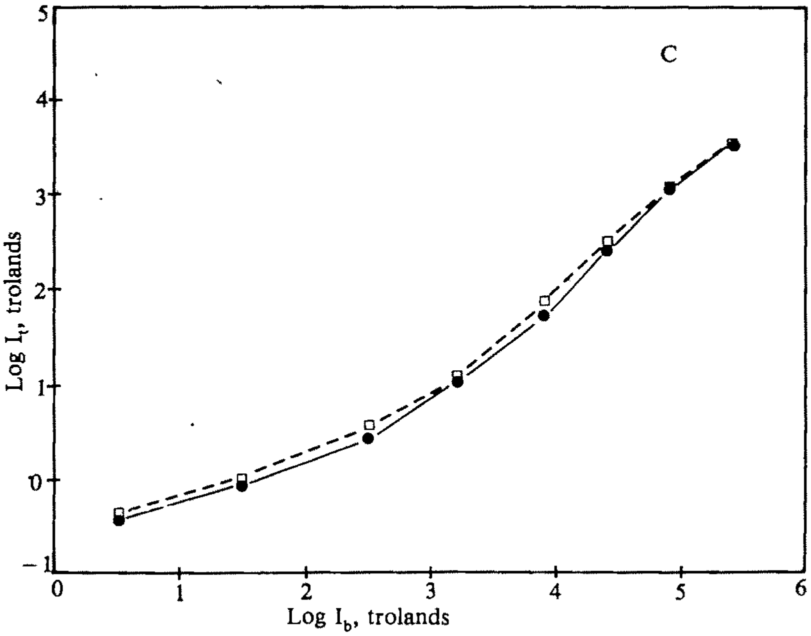


FIG. 6. Log threshold illumination level, log I_t, for detection of a 5.7 degrees diameter circular test target, A, with a 17.5 degrees diameter circular background field of illumination level I_B. The target was presented either as a stationary flash for 250 ms every 2.5 s (squares) or moving at 40 deg/s along the horizontal meridian (triangles). Subject G.Y. (30 degrees off-axis in the blind hemifield). B, as A, but with the target superimposed on a 48 degrees diameter circular background field, of illumination level I_B. C, increment threshold illumination values for a normal subject. V.W. (●) and for the normal hemifield of the hemianopic subject, G. (□). The 5.7 degrees target, flashed for 250 ms every 2.5 s was presented 30 degrees off-axis along the horizontal meridian against a 48 degrees diameter background field of illumination level I_B. Each data point is the mean of 4 to 6 readings with standard errors 0.04 (G.) and 0.03 (V.W.).


B
4.0
3.0
2.0
1.0
Log I_t, trolands
Fixation spot
12°
Test target
30°
48°
□— Flashed target
△— Moving target
−0.5
0.5
1.5
2.5
3.5
Log I_b, trolands


C
5
4
3
2
1
0
−1
Log I_t, trolands
0
1
2
3
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5
6
Log I_b, trolands

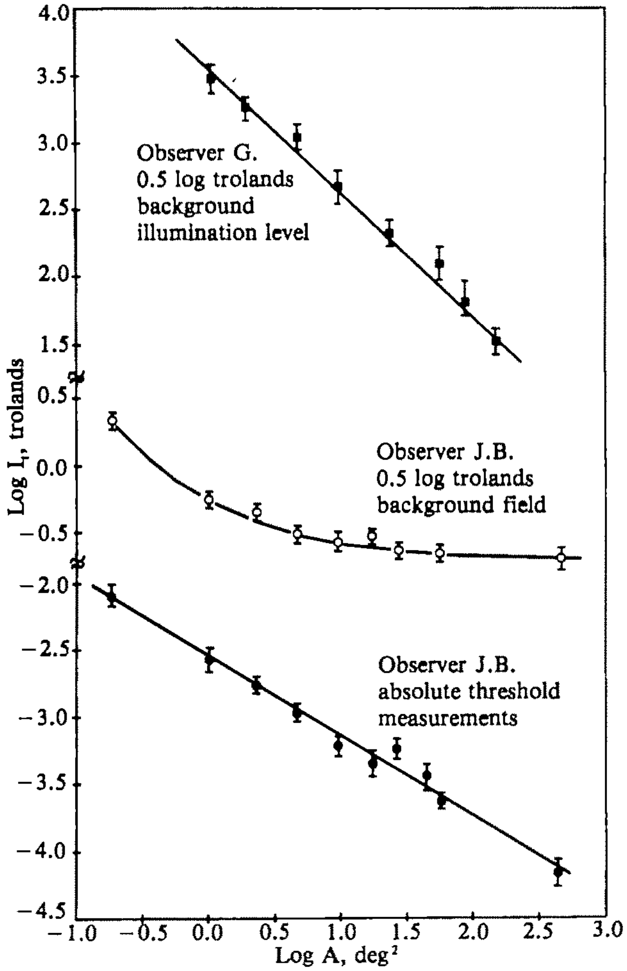

FIG. 7. Log threshold illumination level, log I_t, for detection of a flashed circular target of area A, plotted against log A. The target was presented 30 degrees off-axis and each point represents the mean of 4 to 6 readings, with SD indicated by the bars. ■ = data for subject G. (blind hemifield), measured for a 48 degrees background field of illumination level 0.5 log trolands. The least squares line is given by the relation, $\log I_t = -0.93 \log A + 3.62$ with a correlation coefficient −0.99. ○ = equivalent data for subject J.B., showing variable gradient. ● = data for subject J.B. measured with a dark background field. The least squares straight line is given by $\log I_t = -0.59 \log A -2.54$ with a correlation coefficient of −0.99.

which was either red (628 nm) or blue-green (495 nm). G. was instructed to reduce the illumination level of the moving monochromatic target until it was just no longer detected. The results obtained for G.'s blind hemifield (30 degrees off-axis on the horizontal meridian) are plotted in fig. 8, together with comparison data for the normal subject J.B. The spectral sensitivity curves for subject G. follow closely the absorption spectrum for rhodopsin (for both background illumination levels investigated), which implies that rod signals dominate the responses of the 'blind' hemifield. The comparison data for J.B. show, however, that the normal responses are also dominated by rods, as significant cone contribution leading to a Purkinje shift occurs only at the highest background illumination level of the 495 nm background field (4.3 log units above absolute threshold).

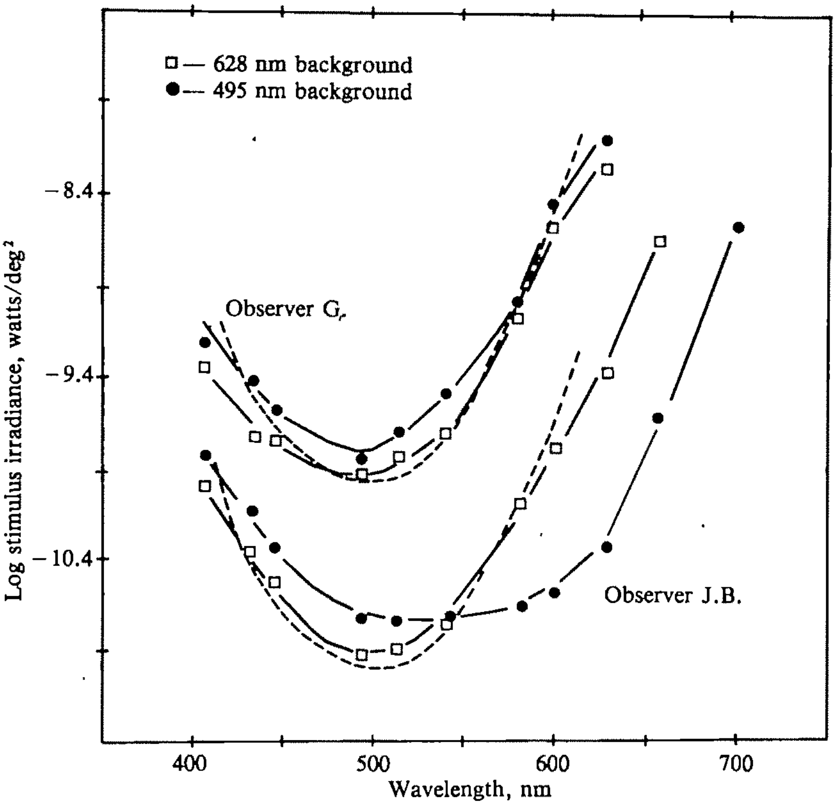

FIG. 8. Threshold irradiance values plotted against stimulus wavelength for detection of a 5.7 degrees diameter circular target presented moving along the horizontal meridian, at 40 deg/s. The target moved through 12 degrees of visual angle, centred 30 degrees off-axis, with a 48 degrees background field of wavelength 628 nm (□) or 495 nm (●). Data for G. (blind hemifield) were obtained for a background illumination level of 1.0 log trolands, whilst those for the normal subject refer to a background illumination level of 3.0 log trolands, in order to bring the threshold settings to comparable irradiation levels. The broken curve shows the spectral sensitivity of the rod (π_0) response mechanism (Wyszecki and Stiles, 1967). Each data point is the mean of 4 to 6 readings, with standard errors 0.04 (G.) and 0.03 (J.B.).

Critical Fusion Frequency

A 5.7 degrees diameter circular target, superimposed on a uniform 0.75 log troland, 48 degrees diameter circular background field, was presented to G.'s blind hemifield (30 degrees off-axis, on the horizontal meridian). The target beam was chopped by a sector shutter, placed at an intermediate focal point, which provided square-wave temporal modulation. The sector shutter was driven by a calibrated, variable-speed servomotor, and G. was instructed to increase the modulation rate, by increasing the motor speed, until he could just no longer detect flicker. The results (fig. 9) show that G.'s flicker response is restricted to very low values ($\leqslant$ 8 Hz), whereas data for the normal subject extend to some 30 Hz. The 8 Hz limit for G.'s flicker frequency response is significantly lower than the saturation value for normal rod vision, which is reported as 15 to 18 Hz (Brindley, Du Croz and Rushton, 1966). Thus, although ability to detect fast moving targets persists, flicker sensitivity in G.'s blind hemifield is significantly reduced relative to that for normal vision.

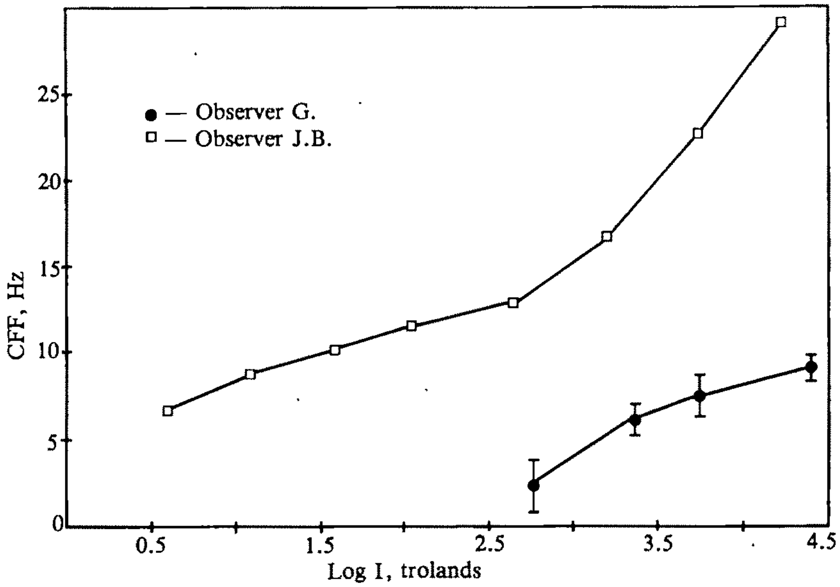

FIG. 9. Critical fusion frequency (CFF) measured as a function of log target illumination level, log I, for a 5.7 degrees diameter circular target presented on a steady 0.75 log troland uniform background field. The stimulus was located 30 degrees off-axis in G.'s blind hemifield (●) and for the normal subject J.B. (□). Each point is the mean of 4 readings and the error bars represent standard deviations.

Discrimination of Spatial Parameters

Experiments were performed to test discrimination of target size, orientation and shape by G.'s 'blind' hemifield. All targets were presented 30 degrees from the fovea, on the horizontal meridian, for a restricted (250 ms) duration and for a limited number of occasions, thus G.'s capacity to learn the tasks was not tested. All discrimination tasks could be performed with 100 per cent accuracy when equivalent tests were carried out by subjects with normal vision. Size discrimination was tested with four circular targets, of diameter 1.5 degrees, 3.5, 5.5 and 8.3 degrees, which were allocated reference numbers 1 to 4, respectively. The targets were firstly viewed foveally, and G. was told the reference number for each target. The targets were then presented in random order, to the 'blind' hemifield, and G. was requested to identify the targets by the appropriate reference number. Measurements were made for two illumination conditions. Firstly, all targets were set at 3.4 log trolands, and the percentage of occasions on which G. correctly identified each target (32 presentations of each) was: 1, 69 per cent; 2, 50 per cent; 3, 44 per cent and 4, 72 per cent, all of which are significantly greater than chance at 0.01 level of significance. The targets were then presented with the illumination level for each adjusted to 0.75 log units above threshold level for its detection. The percentage of correct responses for 32 presentations of each target was: 1, 6 per cent; 2, 9 per cent; 3, 3 per cent; 4, 19 per cent, none of which corresponds to significant recognition. We attribute G.'s ability to identify the first set of targets, all with 3.4 log troland illumination level, to differences in target 'brightness'. Previous data (fig. 7) established large spatial summation for threshold detection in G.'s 'blind' hemifield and thus increase in target area at constant illumination level implies an increase in 'brightness'. When the target illumination levels are adjusted to be at equal suprathreshold level, however, G. is unable to identify target size.

Orientation discrimination was tested with a 12 × 1.35 degrees target, which was orientated vertically, horizontally, or at 45 degrees to the major axes. The target illumination level was 0.75 log units above the threshold for its detection, and it was presented as a 250 ms flash to G.'s 'blind' hemifield (30 degrees off-axis). Target orientation was varied randomly and the percentage of correct identifications for the different orientations (72 presentations of each) was 45 per cent vertical, 21 per cent horizontal and 49 per cent diagonal. The subject studied by Weiskrantz *et al.* (1974) could discriminate orientation of bar-shaped targets presented 10 degrees off-axis, as long as the bar length exceeded a critical, minimum value of some 12 degrees. It is possible that in our experiments the large 30 degrees eccentricity of the targets and their relatively short length (12.5 degrees) may have contributed to G.'s poor orientation discrimination. Indeed, we observed orientation discrimination in measurements with targets located in the 'blind' hemifield, close to the vertical meridian, but we defer presentation of results for such retinal locations until more extensive measurements, accompanied by continuous monitoring of small eye movements, are performed.

Shape discrimination was tested with four targets, each of area 6.6 square degrees and of illumination level 2.7 log trolands, presented against a uniform 48 degrees diameter circular background field of illumination level 0.5 log trolands. The target shapes were a circle, a square, an equilateral triangle and a rectangle (length to breadth ratio 5) and G. first viewed the targets foveally. They were then presented in random order to his 'blind' hemifield (30 degree off-axis) for 250 ms, and he was requested to identify the target shape. The percentage of correct responses (30 presentations of each) was 30 per cent (circle), 27 per cent (triangle), 23 per cent (square) and 23 per cent (rectangle), none of which differs significantly from chance values. Thus G. is unable to perform pattern discrimination under these conditions.

Speed Discrimination

We have shown that G. can detect targets moving across his 'blind' hemifield, and that his sensitivity increases as the target speed increases above 15 deg/s (figs. 4 and 5). We tested G.'s ability to discriminate relative velocity of a 5.7 degrees diameter circular test target, by a forced choice method. He was presented with the target moving at a fixed reference speed 34.5 deg/s, and then with it moving in the same direction, at speed v deg/s. G. was requested to state which target moved faster. The target illumination level was 2.8 log trolands and its location was 30 degrees off-axis in G.'s 'blind' hemifield. Similar measurements were made for the normal subject J.B. The experimental results (fig. 10) are plotted as percentage of occasions on which a test target travelling with velocity v deg/s was identified as moving faster than the reference target, travelling at 34.5 deg/s. It is apparent that G. has speed discrimination similar to that of the normal subject J.B. We considered the possibility that G. used brightness clues to discriminate target velocity. For example, his threshold illumination level for a target speed of 40 deg/s is some 0.3 log units lower than that at 34.5 deg/s, thus as in this experiment all targets were presented at the same illumination level, the 40 deg/s target may have been identified by its greater brightness. We therefore repeated the measurements, with the illumination level of the 40 deg/s target reduced by 0.3 log trolands, so that it was at the same 'supra-threshold' level as the 34.5 deg/s reference target. G. still discriminated the velocities correctly on 100 per cent of presentations, which establishes that he was not using 'brightness' clues in this discrimination task.

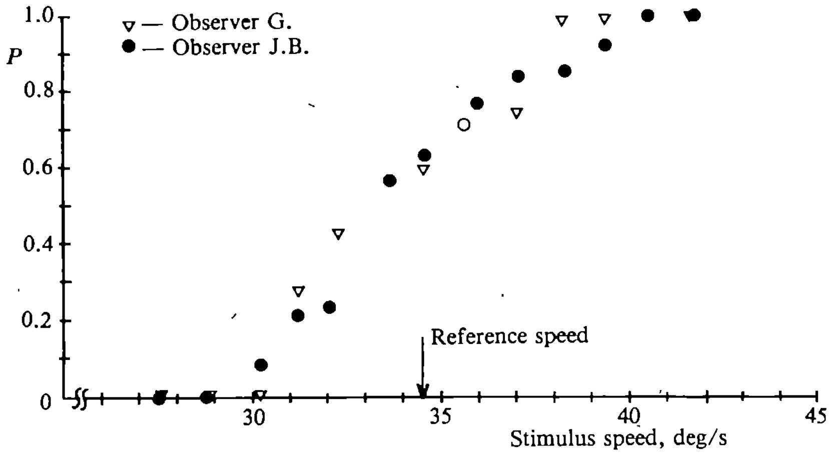

FIG. 10. The probability, *P*, for identifying the speed, V, of a 5.7 degrees diameter circular target as being greater than that of a similar reference target, moving at speed 34.5 deg/s. The target illumination level was 2.8 log trolands, and it was located 30 degrees off-axis. Data for G.'s blind hemifield (▽) and for the normal subject J.B. (●).

DISCUSSION

Light Scattering

One possible explanation of G.'s visual responses to 'blind' hemifield stimulation is that light from the target is scattered into the normal hemifield and detected there. In order to minimize light scattering effects, the test field was in most experiments located 30 degrees away from the fovea and a 48 degrees circular background covered part of the normal hemifield. Nonetheless, a direct test was designed for examination of the light scattering hypothesis. Increment threshold levels, I_t, for detection of a test target superimposed on a 17 degrees diameter circular background field were measured for different background illumination levels I_B, with the normal half-field illuminated at level I_0 (*see inset*, fig. 11A). By determination of the combination of I_0 and I_B which yields the same increment threshold level as when the normal half-field is illuminated at level I'_0, a scattering coefficient K′ can be derived (*see Appendix* for analysis). Experimental increment threshold levels, I_t, are plotted against I_B for different values of I_0 and any pair of these sets of data yields an estimate for K′. On the assumption that G.'s responses arise entirely from light scattered into the normal hemifield, the values of K′ vary between 0.18 and 15.8. These values imply that the effective illumination level, due to scatter into the normal half-field, is between 0.18 and 15.8 times that of the scattering source, located 30 degrees away in the 'blind' hemifield. Light scatter clearly cannot amplify the illumination level relative to that of the source and should give a constant value for the coefficient K′. Threshold illumination levels were also measured for a normal subject, I.H., but in this case the 5.7 degrees diameter test-spot was presented at the fovea (*inset*, fig. 11B). The measurements were made for the same combination of background fields as for G., but the experimental data are entirely different from those of fig. 11A, and the value of K′ is approximately 0.2×10^{-3}. This confirms that scatter from the left half-field cannot raise thresholds in the right half-field by the extent observed for subject G. (*see* fig. 11A).

The data of fig. 11A can also be used to estimate the coefficient K″ for light scatter from the normal into the 'blind' hemifield. In this case, values of K″ range from 0.39 to 5.4, which, as argued above, are inconsistent with a light-scattering hypothesis. The increase in threshold level for 'blind' field detection caused by light stimulation of the normal hemifield (fig. 11A) must, therefore, be attributed to neural interaction between the two hemifields. We note that the small change in threshold level which occurs when the background field size is increased from 17.5 to 48 degrees (fig. 6) is consistent with such an interaction.

Other experimental data presented in the Results section are inconsistent with the view that G.'s 'blind' hemifield sensitivity is caused by scattered light. Thus he is able to identify stimulus location in the 'blind' hemifield and, subjectively, he perceives light flashes presented in the 'blind' hemifield at just suprathreshold illumination levels as dark shadows, whereas equivalent stimulation of the normal hemifield is perceived as brightening in the field. More intense stimulation of the 'blind' hemifield gives a sensation of a well-localized bright flash. Other features of G.'s 'blind' hemifield responses, such as the 8 Hz saturation value for critical fusion frequency and the large linear summation (fig. 7) are quite unlike equivalent data for normal vision.

Visual Field Maps

G.'s visual responses emphasize the influence of presentation mode on the observed visual field map (figs. 1 and 2). Macular sparing has been reported in many other cases involving hemianopic vision (Teuber *et al.*, 1960) and the responsiveness of the 'blind' hemifield was not unexpected, in view of previous studies reviewed in the Introduction (Riddoch, 1917; Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974; Perenin and Jeannerod, 1978). None the less, the present study has revealed a number of new characteristics of non-cortical 'vision' and, in particular, the relatively high sensitivity of such vision to flashed and fast-moving targets (figs. 4 and 5). G.'s ability to identify stimulus location in the 'blind' hemifield (fig. 3) confirms previous reports and implies that there is a topological map of the visual field associated with the surviving, non-cortical response mechanisms.

Signal Transmission Characteristics of the Non-cortical Response Mechanisms

We have presented a number of experimental findings which characterize G.'s responses to targets located 30 degrees off-axis in his 'blind' hemifield. As was noted in the previous section, these responses are restricted to flashed and moving targets, particularly those with velocity > 30 deg/s. Because detailed information about G.'s accident was not available, we cannot be sure that the optic radiation was completely severed, thus we have to concede the possibility that an isolated bundle of fibres responsible for detection of transient stimuli may have survived. As G. can detect such transients at any location in the 'blind' hemifield, however, the ordered topological nature of mapping from the primate lateral geniculate nucleus to the cortex makes it most unlikely that such non-localized responses could be associated with a localized fibre bundle. We therefore propose that G.'s 'blind' hemifield responses are associated with non-striate projection pathways. Flicker fusion response in the 'blind' hemifield is poor, with flicker sensitivity restricted to the very bottom of the sensitivity range for normal vision (fig. 9). In contrast, for the values investigated, G. can discriminate target velocity as well as can a subject with normal vision (fig. 10). Thus detection of temporal modulation associated with a stationary target appears to be quite distinct from detection of target velocity. Spectral analysis shows that responses of the 'blind' hemifield are dominated by rod signals (fig. 8), and the change in increment threshold with increase in background illumination level is similar to that found for the dark-adapted normal eye. The threshold values, I_t, are, however, some 50 times larger for the 'blind' hemifield responses than for normal vision (fig. 6), thus the projection pathway responsible for visual responses arising in the 'blind' hemifield requires considerably greater signal levels for conscious target detection than does the striate cortical projection. Spatial

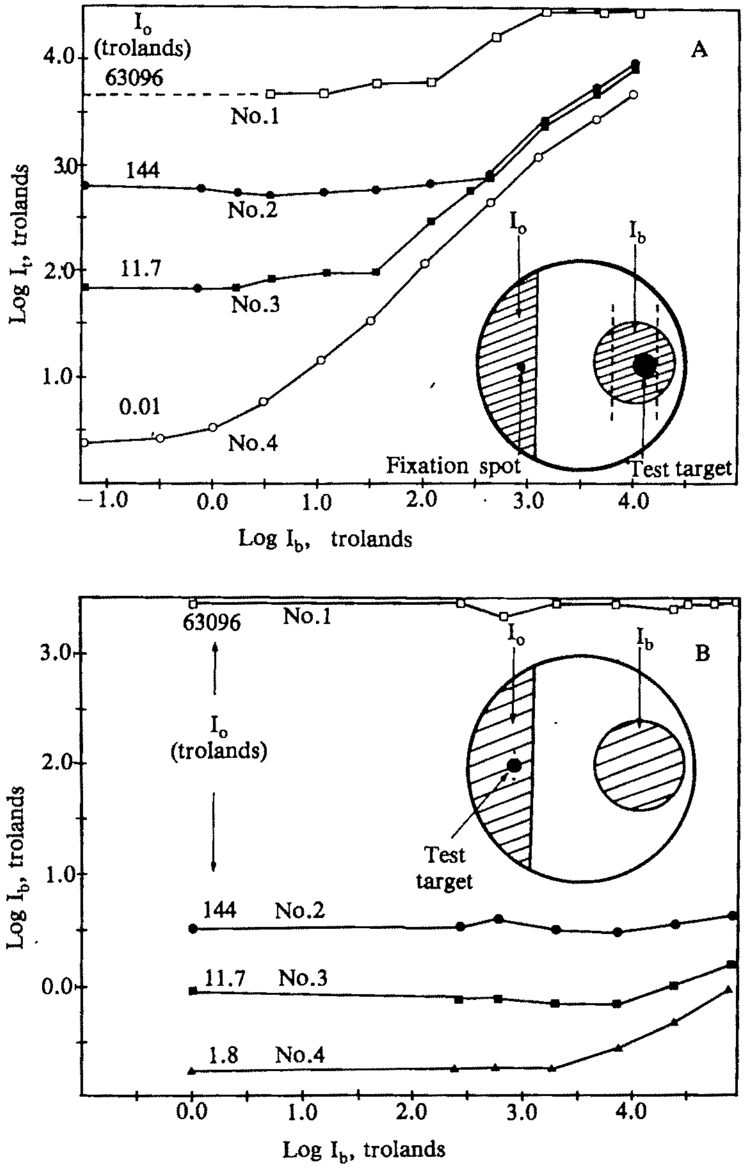

FIG. 11. Log threshold illumination level, log I_t, for detection of a target in the presence of a 17.5 degrees diameter circular background field, of illumination level I_b, centred 30 degrees off-axis in the right hemifield, and with the left hemifield uniformly illuminated at level I_0. The subject fixated 5 degrees within the uniformly illuminated left half-field, which ensured that G.'s spared foveal right half-field area was covered by this half-field. A, data for subject G. the 5.7 degrees diameter test, moving at 40 deg/s along the horizontal meridian, through 10 degrees of visual angle centred 30 degrees off-axis. Each set of data refers to a different value of I_0, as indicated at the left of the data curves. Each point is the mean of 4 readings, with typical standard error 0.05. Values of the scattering coefficient K′, estimated for different pairs of curves, were 15.8 (curves 1 and 2), 15.8 (curves 1 and 3), 6.3 (curves 1 and 4), 0.55 (curves 2 and 3), 0.24 (curves 2 and 4) and 0.18 (curves 3 and 4). B, data for normal subject I.H. The 1.5 degrees diameter circular test target was located 5 degrees from the edge of the uniform illumination level in the left half-field, and its location was marked by two fixation points, as indicated. The target was flashed for 250 ms every 2.5 s and the value of I_0 for each set of data curves is indicated to the left. Each point is the mean of 5 readings, with typical standard error 0.03. The scattering coefficient, K′, for curves 3 and 4 was equal to some 0.2×10^{-3}.

summation for threshold detection is linear over a very large range of target areas (fig. 7), a result which merits further investigation in view of the non-linear relation between voltage response amplitude and stimulus illumination level observed in vertebrate photoreceptors (*see* Schwartz, 1977). Correlating with this large summation at threshold, G.'s discrimination of spatial paramaters for suprathreshold illumination targets was poor. He appears to differ in this respect from the subject studied by Weiskrantz and co-workers, who was well able to differentiate target orientation and fine spatial structure. Our failure to observe spatial discrimination may be a consequence of the target location (30 degrees off-axis) chosen for this study, or of the response criterion employed (*see* Methods). Some features of G.'s 'blind' hemifield responses do, however, imply relatively fine spatial resolution. Thus, he can detect apparent motion between targets separated by only 3 degrees of visual angle and he can localize targets to within some 4 degrees (fig. 3). Our experimental results show that the mechanisms which mediate such spatial discriminations do not, however, give rise to pattern recognition.

Comparison Between Response Characteristics of G.'s 'Blind' Hemifield and Those of Units in the Superior Colliculus

Ablation studies have shown that animals from which the cortex to which the dorsal lateral geniculate nucleus projects is removed can still perform visual discriminations as long as the superior colliculus is intact (*see* Sprague, 1966; Schneider, 1969; Weiskrantz, 1972; Mohler and Wurtz, 1977). Consequently, it is usually assumed that in humans with cortical lesions, visual responses which can be elicited from field areas projecting to the damaged cortical region reflect activity in the collicular pathway. We have, therefore, compared the response characteristics of G.'s 'blind' hemifield with those of collicular units. G.'s ability to locate targets flashed in the 'blind' hemifield (fig. 3) correlates with the field map observed in superficial layers of the superior colliculus. Collicular units are selectively sensitive to flashed or moving stimuli (Schiller and Koerner, 1971; Goldberg and Wurtz, 1972) and their sensitivity increases with increase of target velocity, up to some 50 deg/s. There is, therefore, good correspondence between the responses of single collicular units and the psychophysical data (figs. 4 and 5). Other features of collicular responses which are reflected in G.'s responses include large spatial summation which is comparable with neuronal receptive fields of up to 225 degrees^2 (Marrocco and Li, 1977), and absence of orientation selectivity. G.'s psychophysical data (fig. 8) show that his 'blind' hemifield responses, 30 degrees off-axis, are dominated by rod signals, whereas responses of single collicular units show clear evidence of cone activity (Marrocco and Li, 1977). The electrophysiological data, however, were obtained largely ($\sim$ 85 per cent) within 25 degrees of the fovea, thus they are not strictly comparable to our psychophysical results. One important feature of the present data which merits electrophysiological investigation is G.'s low sensitivity for target detection in the blind hemifield (fig. 6). Direct comparison of threshold sensitivities in responses of single cortical and collicular units could help to decide whether the large increment threshold values of G.'s 'blind' hemifield reflect an inherent property of the superior colliculus, or whether they are associated with more central pathways. Other pathways which may contribute to G.'s responses include the pre-tectal projection controlling pupil reflex and the accessory optic system which is critical for 'light-dark' discrimination in destriate monkeys (Pasik and Pasik, 1971).

The Significance of the Experimental Data for the Two-system Analysis of Visual Function.

As was discussed in the Introduction, it has been proposed that visual spatial orientation is controlled by the collicular pathways and detailed pattern discrimination by the geniculo-cortical pathway. We have shown that G. can detect and locate moving and flashed targets within his 'blind' hemifield, but cannot discriminate the spatial patterns associated with these stimuli. In the previous section, we reviewed evidence which favours the hypothesis that G.'s visual responses for the 'blind' hemifield are due to collicular activity. Thus the present results are broadly consistent with the 'two systems' analysis of visual function. The close similarity in velocity discrimination of G.'s 'blind' hemifield and that of normal vision suggests a common response mechanism. Such a mechanism could be provided by the transient (Y-) ganglion cells, which project to both the superior colliculus and the lateral geniculate nucleus. Alternatively, it may be that the responses of the normal subject reflect activity in the collicular pathways.

SUMMARY

This paper describes an investigation of responses elicited by flashed and moving light stimuli presented to the 'blind' half-field of a hemianopic subject. The detection mechanism is significantly less sensitive than that for vision in the normal half-field, but the increment threshold varies with the background illumination level in a manner similar to that for normal vision. The responses of the 'blind' hemifield are characterized by low critical fusion frequency ($\leqslant$ 8 Hz), large spatial summation and high sensitivity to fast moving targets. Velocity discrimination for targets located in the 'blind' hemifield is normal, but neither the shape nor the size of the target is discriminated. It is shown that the experimental data cannot be attributed to light scattered from the 'blind' into the normal hemifield, and other mechanisms which may be responsible for the observed responses are examined.

ACKNOWLEDGEMENTS

We are indebted to G., the subject of this study, who during his spare time has voluntarily undertaken a long and arduous series of observations. We also wish to thank Dr T. D. H. Gray for providing information on G.'s ophthalmic history, Professor L. Weiskrantz for most helpful comments on the manuscript and our colleague Mr I. Holliday for assistance in some measurements. V.A.W. acknowledges with thanks the award of a Science Research Council studentship.

APPENDIX

Test for Scattered Light

The stimulus configuration is shown in the inset of fig. 12. The normal left half-field is uniformly illuminated at level I_0 (or I_0') and the 5.7 degrees diameter target moved horizontally at 40 deg/s. The target, T_h, moved through the central 10 degrees of a 17.5 degrees diameter background of illumination level I_B, centred 30 degrees off-axis along the horizontal meridian in the 'blind' hemifield. For a given value of I_0, I_t is measured as a function of I_B, yielding data of the form shown in curve A (fig. 12.) For some other illumination level in the left half-field, I_0' ($> I_0$), the curve B is obtained. Now consider that threshold detection occurs at some unspecified point in the normal hemifield as a result of light scattered from the target into the normal hemifield. Let the effective target illumination level at the point of detection due to light scatter be KI_t, where I_t is the target threshold illumination level. Then the scattered light due to the background field will be $K'I_B$, thus for normal hemifield illumination level I_0, the total background against which the target is detected is $(I_0 + K'I_B)$. There will be some other level, I_0', at which the uniform field in the left half-field produces the same threshold illumination level, I_t, as that found for the combination of I_0 and I_B, but with the target located on a dark background (*see* fig. 12). Thus, the background illumination levels are equivalent under these two conditions, giving:

$$I_0' = I_0 + K'I_B$$

so K′ can be found as $(I_0' - I_0)\, I_B$. Measurements can be made for different values of I_0, and as the background field spatial configuration is constant, the coefficient K′ should be the same for all background illumination levels. The value of K′ was estimated directly by performing similar

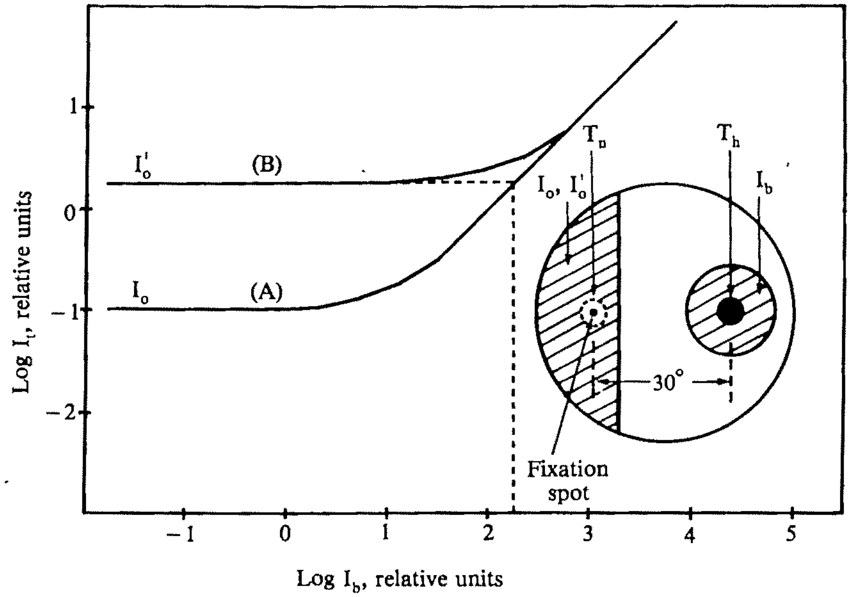

FIG. 12. Schematic values for log threshold illumination, log I_t, plotted against log illumination level of the 17.5 degrees diameter field, located 30 degrees off-axis in the right hemifield. The left hemifield was uniformly illuminated at level I_0, and this extended for some 5 degrees across the vertical meridian, that is, the fixation point was located 5 degrees within the uniformly illuminated region. The graph illustrates the derivation of the scattering coefficient K′. For subject G., the moving target, T_h, was located at the centre of the 17.5 degrees background field, whereas for the normal subject J.B., the flashed test target, T_n, was located at the fixation point.

experiments with a normal subject, except that in this case, the target was presented in the left half-field (target T_n, *inset* fig. 12).

If it is assumed that the hemianopic subject detects the target with his 'blind' hemifield and that illumination of the left half-field influences thresholds in the 'blind' hemifield by light scatter, then a coefficient K″ for this process can be derived in a manner analogous to that described above for K′.

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THE PATHOGENESIS OF ISCHÆMIC NEURONAL DAMAGE ALONG THE CEREBRAL ARTERIAL BOUNDARY ZONES IN *PAPIO ANUBIS*

by J. B. BRIERLEY, PAMELA F. PRIOR, JANE CALVERLEY,
S. J. JACKSON *and* A. W. BROWN

(From the Medical Research Council Laboratories, Carshalton, Surrey SM5 4EF, Department of Neurological Sciences, St. Bartholomew's Hospital, London EC1A 7BE and Cardiovascular-Pulmonary Unit, Department of Medicine, Charing Cross Hospital Medical School, London W6 8RF)

INTRODUCTION

A CONCENTRATION of ischæmic neuronal destruction along the arterial boundary zones of the human brain has been described as a consequence of systemic hypotension due to myocardial insufficiency (Adams, Brierley, Connor and Treip, 1966), dental anæsthetic accidents in the upright position (Brierley and Miller, 1966), moderate hypotension in hypertensive subjects (Graham, 1975) and in patients suffering non-missile head injuries (Graham, Adams and Doyle, 1978).

In most of the above instances, spontaneous respiration did not fail and the common pathogenetic factor was reduced cerebral perfusion usually due to a considerable reduction in systemic blood pressure. Some additional hypoxæmia may have been present in a proportion of cases. In spontaneously breathing, normoxæmic experimental primates it has not been possible to produce ischæmic damage along arterial boundary zones by hypotension alone until the point of apnœa has been reached. Thus, in normoxæmic *Macaca Mulatta*, when systemic blood pressure was reduced by a ganglion blocking agent together with head-up tilt of the table and bleeding, apnœa occurred sooner or later and mechanical ventilation was required to maintain normal arterial oxygen tension. Only then was the period of uncomplicated hypotension long enough to produce brain damage (Brierley, Brown, Excell and Meldrum, 1969—animals of Group II).

In *Papio Anubis* one or two exposures to profound hypoxia (PaO_2 17.2 ± 2.4 mmHg) also led to apnœa in 89 to 205 s (that is, times to 'last breath') and the EEG was then isoelectric. Prompt mechanical ventilation restored circulation, respiration and the EEG. The brain was always normal as the period of hypoxia-ischæmia was too brief to damage neurons irreversibly (Brierley, Prior, Calverley and Brown, 1978*a*). In this study it was shown that similar hypoxic exposures in the rhesus monkey ended in a typical cardiorespiratory crisis with the 'last breath' at 93 to 570 s. A single animal submitted to 4 such exposures within 75 min showed a minor neurological deficit. It was killed by *in vivo* perfusion-fixation at six days. In the same study preliminary exposure of monkeys to 14 per cent oxygen (PaO_2 53 ± 7 mmHg, $n = 15$) for about 26 min significantly extended the time to apnœa. In one animal the 'last breath' was postponed until 94 min and was preceded by a period of falling heart rate and blood pressure. Mechanical ventilation was required for a few seconds and there was obvious neurological impairment up to perfusion-fixation at 22 h. In these 2 monkeys brain damage was similar in nature and distribution. It took the form of ischæmic cell change with the gliomesodermal reaction appropriate for the survival time and the amount of neuronal destruction. The distribution was restricted to the arterial boundary zones of the cerebral cortex in each animal but additionally along those of the cerebellum of the second.

The study demonstrated that profound hypoxia *per se* cannot produce damage in the brain of the spontaneously breathing baboon or rhesus monkey. Exceptionally, as in the 2 animals described, a repetition or a prolongation of the final hypoxic cardiorespiratory crisis could result in ischæmic damage along boundary zones. It was obvious that in order to obtain such damage reproducibly in the brains of experimental primates without the complication of respiratory failure, a lesser degree of hypoxia would have to be combined with some method of reducing cerebral blood flow uni- or even bilaterally that did not impair cardiac function during the stress itself and particularly during recovery.

This communication describes a physiologically monitored survival preparation in the baboon in which spontaneous respiration is unimpaired and in which brain damage is invariably along the arterial boundary zones of the cerebral cortex but may also be present in the basal ganglia. The preparation was developed from that of Levine (1960) in the rat in which occlusion of one common carotid artery with additional hypoxia results in largely ipsilateral ischæmic brain damage (Levine, 1960; Brown and Brierley, 1968).

In the lightly anæsthetized baboon an arterial PO_2 in the range 20 to 24 mmHg was found to be the lowest compatible with the retention of spontaneous respiration. Occlusion of one common carotid artery during this hypoxæmia was, with one exception, without effect on the EEG. After additional occlusion of the other artery, spontaneous respiration was maintained so that the EEG was the only index of alterations in forebrain function. Sooner or later the EEG became isoelectric and the severity of the resulting brain damage was related to the duration of the isoelectric period together with the rate of EEG recovery. After restoration of carotid flow and resumption of air breathing there was evidence of immediate cerebral hyperperfusion and no significant systemic hypotension occurred during the recovery period.

Using this preparation it has been possible to show that after periods of up to 8 min of isoelectric EEG during bilateral carotid occlusion with hypoxia clinical recovery is complete and the brain always undamaged. If this period is exceeded brain damage will occur and the minimal lesion lies in the cortex in the depths of the intraparietal sulcus, the junction of the three cortical arterial territories.

A preliminary account of this study has been published (Brierley *et al.*, 1978*b*).

MATERIALS AND METHODS

Twenty adult *Papio Anubis* (weight range 6.5 to 12.0 kg) of either sex were used.

Each experiment was carried out in two stages with a five- or six-day interval (Brierley and Excell, 1966; Brierley *et al.*, 1969, 1977, 1978*a*). The animals were fasted overnight and aseptic conditions with antibiotic cover were used for the first stage but not for the second as survival was deliberately restricted to 48 h.

Stage I

Under pentobarbitone anæsthesia (45 mg/kg intraperitoneally) an indwelling aortic cannula was inserted *via* a femoral artery. The skull was trephined anterior to the torcula for subsequent blood sampling and venous sinus pressure recording from the superior longitudinal sinus. Silver-silver chloride epidural ball electrodes (2 parasagittal rows of 7, one omitted for an intracranial pressure transducer in 17 animals, each row 13 mm from the midline with inter-electrode distances of 10 mm) were connected to a microconnector mounted on the skull to record the EEG. In 18 animals a pair of intracerebral glass-insulated tungsten steel electrodes (125 μ diameter, 125 μ exposed tip) were placed stereotactically (co-ordinates, posterior 5 mm and lateral 10 mm for one and posterior 9 mm and lateral 8 mm for the other; the tip of each electrode was 15 mm below the dura) in the floor of the left intraparietal sulcus (fig. 1) which is the junction of the boundary zones of the anterior, middle and posterior cerebral (ACA, MCA and PCA) arterial territories.

In 17 animals a left frontal trephine hole (12 mm diameter) was made to receive a plastic adaptor for recording epidural intracranial pressure (ICP) during Stage II.

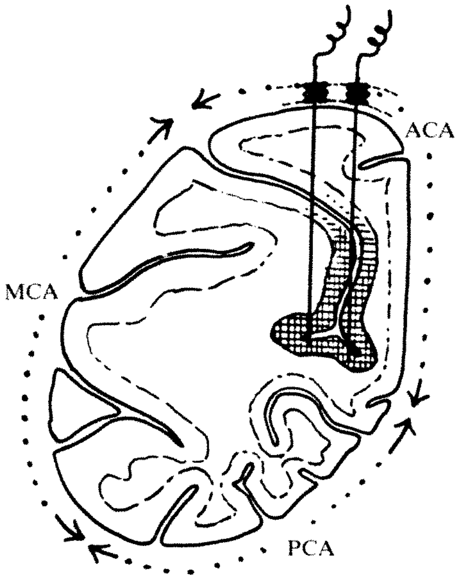

FIG. 1. Coronal section of left occipital lobe showing stereotactically-placed depth electrodes in floor of intraparietal sulcus (junction of the three arterial boundary zones). Shading indicates site of minimal lesion (No. 16).

Stage II

Anæsthesia was induced with intraperitoneal pentobarbitone (45 mg/kg) and atropine 0.6 mg was injected intramuscularly. A cuffed endotracheal tube was inserted. When preparations for physiological monitoring were completed a continuous, mechanical, intravenous infusion of the standard solution of the steroid anæsthetic alphaxolone-alphadolone (Althesin, veterinary preparation, Saffan, Glaxo) was regulated (rates ranged from 0.02 to 1.13 ml/kg/hr) to maintain the EEG features of light to moderate anæsthesia (Prior, Maynard and Brierley, 1978). If anæsthesia became unduly light supplementary boluses of 0.2 to 0.3 ml were given.

Physiological monitoring (details in Brierley *et al.*, 1977) before, during and after the several phases of the experiment included the epidural and depth EEG, ECG, heart rate (audible signal, digital and polygraphic display), respiratory rate and excursion (from pressure transducer attached to side-arm in the endotracheal tube), arterial and venous sinus blood pressures. All pressure transducers were later set at the level of the external auditory meati during hypoxia and carotid occlusion (animals supine). Inspired (I), end-tidal (ET) PO_2 and ET PCO_2 were recorded in all animals using Beckman gas analysers connected in series and drawing their samples through a fine cannula within the endotracheal tube.

The plastic intracranial pressure adaptor was inserted in the trephine hole, filled with water and connected to a pressure transducer. A three-way tap, attached to the latter, was opened briefly so that 'O' pressure was recorded on the dynograph. All subsequent changes in intracranial pressure were related to this arbitrary 'zero' and this channel, like that recording venous sinus pressure, was calibrated in mm water.

The animal was turned into the supine position and for the remainder of the experiment the head was supported between the ear plugs of the stereotactic apparatus. With the head in moderate extension, the common carotid arteries were exposed through a midline skin incision and after division of the superior belly of each omohyoid muscle. The arteries were carefully cleaned and a plastic and aluminium screw-operated clasp was placed around each vessel and left in the open position. The clasp, when closed, ensured that pressure was applied along a 1 cm length of the artery (fig. 2). As the occluding members of the clasp were made of Perspex, total arrest of flow on closure and its immediate resumption on opening could be verified by naked-eye examination. Subsequent histological examination showed that the arterial endothelium was undamaged.

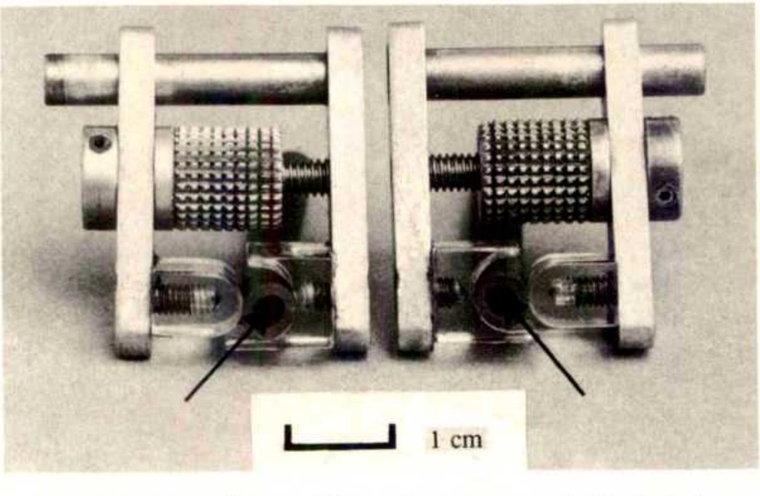

FIG. 2. The right and left carotid artery clasps. Arrows = simulated arteries.

The bipolar recordings of EEG background activity were rated visually by one author (P.F.P.) on a six-point scale (1 = continuous activity, 2 to 5 = increasing burst suppression activities, 6 = isoelectric trace) and also by computer analysis of the tape recorded tracings (Prior *et al.*, 1978). Scores 1 and 2 characterized the light levels of anæsthesia used. A total score for the period of EEG depression was derived by summing the minute-by-minute scores during the periods of carotid occlusion and recovery when the score was 4 or more. A similar score was obtained independently from computer analysis of the tape recorded EEG (derived from the left parietal convexity) in 14 animals. The analysis produced a histogram of the numbers of occurrences of periods of EEG flattening during consecutive 1 min epochs.

Body temperature was recorded continuously from either a rectal or an œsophageal thermistor and was maintained at 37 to 37.5° C using a heated table or an electric blanket.

Blood gases and pH were measured with a Radiometer, Copenhagen, Blood-Micro System in simultaneous samples of arterial and venous sinus blood. In 14 animals lactate and pyruvate contents were estimated in corresponding blood samples (details in Brierley *et al.*, 1977).

The Experimental Sequence

1. *Sequential common carotid artery occlusion breathing air* (*13 animals*). The left common carotid artery was occluded and after 15 min the right also. After a further 15 min both clasps were released simultaneously. This procedure was designed to assess the effects of uni- and bilateral carotid occlusion on systemic blood pressure, intracranial pressure, venous sinus pressure, heart rate, respiration and the EEG.

2. *Sequential common carotid artery occlusion during hypoxia* (*18 animals*). Hypoxia began when the cuffed endotracheal tube was connected to the stem of a T-piece at the bottom of a loop of wide-bore plastic tubing vented through a window. This was done after an interval of 20 to 87 min in those animals already subjected to carotid occlusion while breathing air. Nitrogen flowed through the tube at 3 to 4 l/min and oxygen was added through a Y-piece using an accurate flowmeter adjusted to give a PIO_2 (dry gas) of 57 to 65 mm O_2 on the digital display of the oxygen analyser (fig. 3). This mixture flowed for several minutes before connecting the endotracheal tube.

After the first 20 min of hypoxia (2 to 3 blood samples) the left common carotid artery was occluded and 2 to 3 blood samples were taken during a 20-min period (one exception—No. 5).

The clasp on the right carotid artery was then closed while hypoxia was maintained and the rate of Althesin infusion was unchanged. The initiation and rate of EEG decline to an isoelectric trace defined the number of blood samples that could be taken. After a chosen duration of isoelectric EEG, the arterial clasps were released simultaneously and air breathing was resumed by disconnection of the endotracheal tube from the gas flow. Blood samples were taken from 5 to 61 min after release of the clasps. Physiological monitoring (including the EEG) was continued for about 30 min if EEG recovery was rapid and brain damage, therefore, probably minor or even absent, but for up to 3½ h if EEG recovery was delayed. The animal was returned to the cage when the 'gag' reflex had returned and extubation was possible.

3. *Follow-up and neuropathological examination.* After a survival of 14 to 46 h during which neurological assessment was made, light anæsthesia was induced with Althesin (1 ml/kg intramuscularly) and a follow-up EEG was recorded. Abnormalities in each were graded as mild, moderate and severe. Then, under deep pentobarbitone anæsthesia in the fully heparinized animal, perfusion-fixation with FAM (formaldehyde, glacial acetic acid, absolute methanol, 1:1:8, 3,000 to 3,500 ml in 20 to 25 min) was carried out at a pressure of 150 to 160 mmHg after clamping the descending thoracic aorta and a brief washout with saline. The brain was removed 2 h later. After detaching the hind-brain, the cerebral hemispheres were cut in 8 mm slices in the stereotactic coronal plane. Alternate blocks from occipital to frontal poles and from one cerebellar hemisphere were embedded in paraffin and the remainder including five levels from the brain-stem were embedded in low viscosity nitrocellulose.

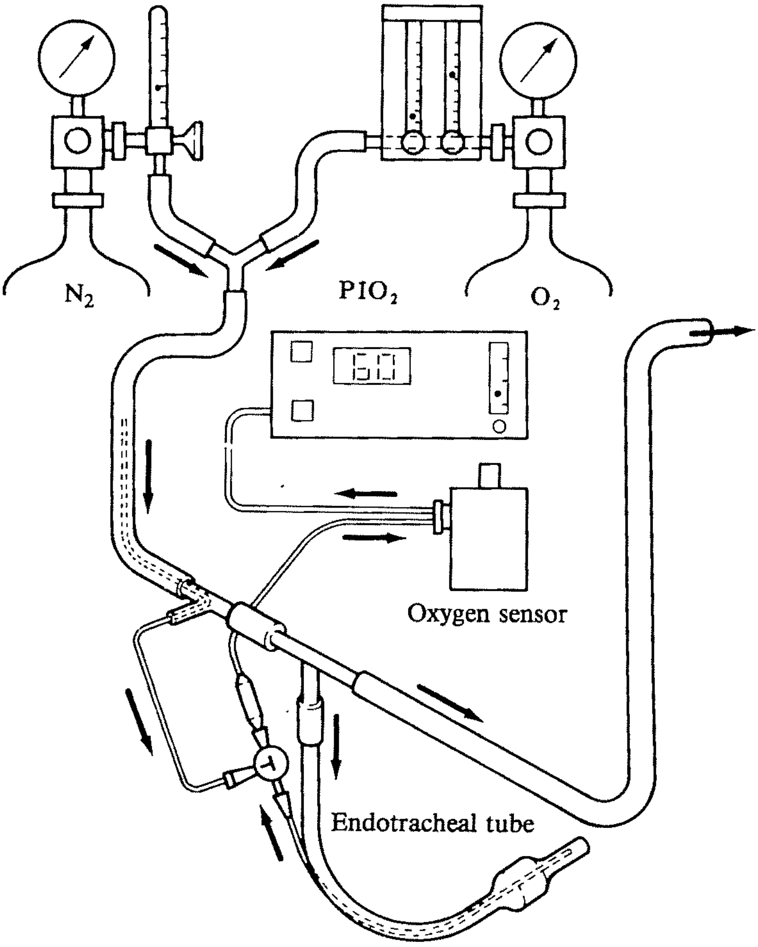

FIG. 3. Hypoxia begins when the endotracheal tube is connected to the T-piece in the open-circuit flow of the nitrogen-oxygen mixture. The oxygen analyser (PIO_2—digital display) is used to determine the oxygen tension in the gas mixture (*via* catheter on left) or within the endotracheal tube. Samples from the latter also pass through an ET CO_2 analyser (not shown).

Paraffin sections were stained with cresyl violet, cresyl violet and Luxol-fast blue, Mallory's phosphotungstic acid hæmatoxylin and with hæmatoxylin and eosin. Celloidin sections were stained additionally with Woelke's modification of Heidenhain's method for myelin sheaths.

As the only neuronal alterations observed were some stages of ischæmic cell change these were graded by one author (J.B.B.) as follows: 0 = normal, 1 = a few neurons involved, 2 = moderate numbers involved and 3 = a majority involved. In view of the fact that these neuronal alterations were restricted to portions of the arterial boundary zones within the cerebral cortex, but sometimes occurred additionally in the caudate nucleus, putamen and globus pallidus, damage in each brain was scored as follows: each ACA/MCA boundary zone lesion was assessed in four standard stereotactic planes, occipital, parietal, central and frontal, and the MCA/PCA boundary zone only in the central (A.10) plane. Within each boundary zone, grading took account of the coronal extent of damage as well as the proportion of neurons involved in any unit area. The basal ganglia were assessed according to similar criteria in central (A.10) and frontal (A.26) planes.

In each hemisphere the maximum brain damage score was

ACA/MCA boundary zone	4 × 3 = 12
MCA/PCA boundary zone	3 = 3
Caudate nucleus, putamen and globus pallidus	3 × 3 = 9
Hemisphere total	= 24
Bilateral total	= 48

As asymmetry of damage was frequent the damage scores for each hemisphere were assessed separately.

RESULTS

Control Values (20 Animals)

A physiological steady state at normothermia was maintained for at least 1 h before sequential common carotid artery occlusion breathing air. Control values for the range of physiological data recorded are shown in Table 1.

TABLE 1. CONTROL PHYSIOLOGICAL DATA IN 20 *PAPIO ANUBIS*

Respiration/min	28.5±5.6 (20–40)
Heart rate/min	160±17.3 (124–194)
Mean arterial BP (mmHg)	133±13.4 (106–148)
PaO_2 (mmHg)	70.8±7.1 (60.2–83.4)
PvO_2 (mmHg)	42.5±4.3 (n = 17; 35.6–49.2)
$PaCO_2$ (mmHg)	40.4±3.5 (33.8–46.0)
$PvCO_2$ (mmHg)	45.3±3.3 (n = 17; 40.7–51.0)
a pH	7.410±0.023 (7.376–7.454)
v pH	7.381±0.021 (n = 17; 7.351–7.423)
*a plasma lactate (mmol/l)	0.98±0.035 (n = 15; 0.39–1.50)
†a plasma pyruvate (mmol/l)	0.061±0.022 (n = 10; 0.026–0.096)

Means and 1 SD are given with range in brackets and n if other than 20. * Including 5 samples at 2 to 12 min after bilateral carotid occlusion breathing air which were within the range of the other 10. † Including one sample similar to the 5 above.

Sequential Common Carotid Artery Occlusion Breathing Air (13 Animals)

After occlusion of the left common carotid artery the earliest and most marked effects were on mean arterial blood pressure (mean arterial BP). This increased in all animals but to a very variable extent (range 3 to 23 per cent). The mean initial peak and the mean level at 15 min are shown in fig. 4. Peak values were attained (mean increase 12 ± 6 per cent) after 12 ± 8 s (range 5 to 30 s). Appreciable increases in heart rate occurred only in Nos. 26, 27 and 28. A brief increase in respiratory rate and depth was indicated in 8 animals by a slight fall in ET PCO_2. An immediate fall of up to 20 mm H_2O in intracranial pressure occurred in all animals and was the most sensitive indicator of the instant of effective common carotid artery occlusion. Slightly smaller reductions in venous sinus pressure were seen in all animals.

After additional occlusion of the right common carotid artery the principal effect was again on mean arterial BP which usually rose to a greater extent (mean increase 17 ± 10 per cent) than after occlusion of the left artery (fig. 4). At the end of 15 min of bilateral common carotid artery occlusion mean arterial BP was always greater than the control value. In 4 animals the peak systolic pressure exceeded 200 mmHg. In No. 14 a peak mean arterial BP of 187 mmHg and in No. 28 a peak of 210, that is 284/174 mmHg produced no disturbance of cardiac rhythm. In No. 26 with a peak mean arterial BP of 175 mmHg, cardiac arrhythmia, consisting of missed beats progressing from 1 in 4 to a pulsus alternans, began after 10 min of bilateral occlusion and both clasps had to be released at 12 min to avert cardiac failure. In

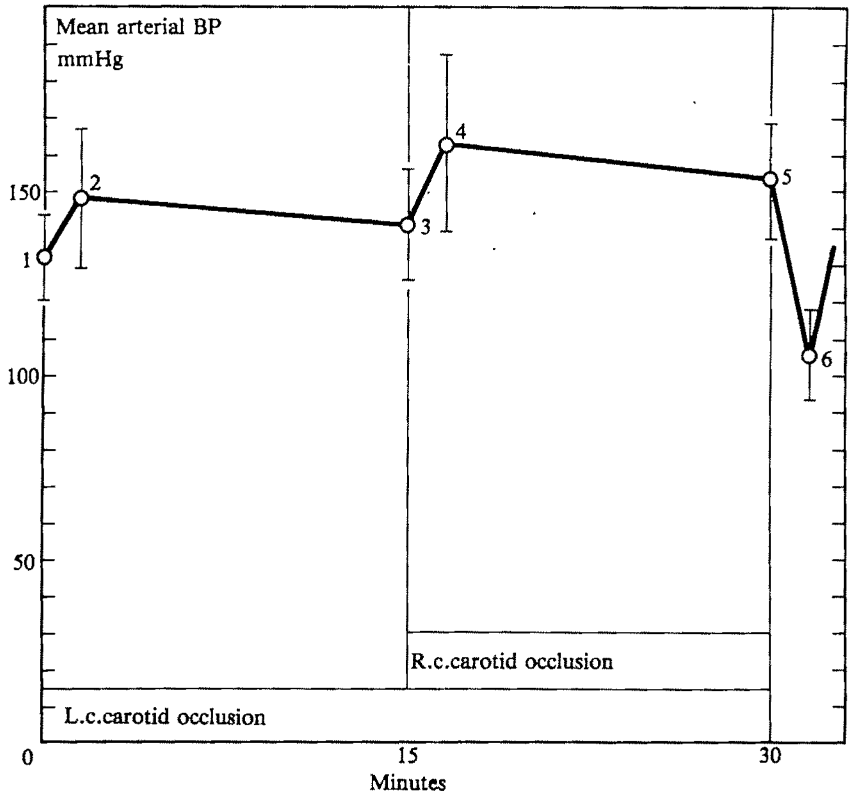

FIG. 4. The course of mean arterial blood pressure (MABP) during and after sequential common carotid occlusion (CCO) while breathing air (mean ± 1 SD, n = 13). Times of events 2, 4 and 6 not to scale. 1 = normal, 2 = peak MABP at 12 ± 8 s after left CCO, 3 = MABP just before right CCO, 4 = peak MABP at 10 ± 3 s after right CCO, 5 = MABP just before release of both artery clasps (n = 11, cardiac arrhythmias in 2 animals necessitated premature arterial release), 6 = minimum MABP at 12 ± 4 s after bilateral CC release (n = 11).

No. 27, with a peak mean arterial BP of 196 mmHg, a similar arrhythmia began at 1½ min and the clasps had to be released 2 min later. This animal was not exposed to subsequent hypoxia. In these last 2 animals a relative depression of EEG activity from the depth electrode (and additionally from the convexity in No. 26) occurred throughout the periods of cardiac arrhythmia although the mean arterial BP remained unchanged. In both, normal cardiac rhythm was resumed at the moment of bilateral carotid release. In all 4 animals the hypertension was sustained during carotid occlusion and the final mean arterial BPs were 172, 179, 170 and 173 mmHg, respectively. An early fall in ET PCO_2 in 5 animals indicated transient hyperventilation.

The immediate fall in intracranial pressure after the added occlusion of the right carotid artery was usually greater (maximum 60 mmH_2O) than after occlusion of the left carotid artery alone and was associated with a slightly lesser fall in venous sinus pressure. The EEG was unaltered during uni- and bilateral common carotid artery occlusion (breathing air) except in animals Nos. 26 and 27 described above. There were no significant increases in lactate and pyruvate contents during 8 to 16 min of bilateral carotid occlusion in the 3 animals with appropriate samples.

In the 11 animals in which the arterial clasps were released at 30 min the mean arterial BP before release was then always greater than the control level (fig. 4). The mean net increase was 22 ± 10 mmHg, that is a mean increase of 17 ± 8 per cent. After simultaneous release of both clasps there were immediate effects on mean arterial BP, heart rate, respiratory rate, intracranial and venous sinus pressure, all without effect on the EEG. Mean arterial BP (fig. 4) fell abruptly to a mean of 106 ± 12 mmHg at 12 ± 4 s. This was usually followed by an almost immediate rapid rise to near normal levels at 5 min. The fall in mean arterial BP was accompanied by a decrease in heart rate (7 ± 3 per cent) and in respiratory rate (27 ± 15 per cent). Both then rose more or less parallel to the mean arterial BP. A sharp rise in intracranial pressure (mean net rise 45 ± 36 mmH_2O) indicated the precise time of common carotid artery release and the venous sinus pressure followed a parallel course.

Sequential Common Carotid Artery Occlusion during Hypoxia (18 Animals)

In the 15 animals in which blood samples at 5 min were available, mean PaO_2 was 21.2 ± 2.5 mmHg. Hypoxia lasted for a mean of 22 ± 5 min ($n = 18$). There was immediate hyperventilation with a mean peak respiratory rate of 37 ± 7/min ($n = 16$) which had fallen to 34 ± 7/min ($n = 18$) by the end of hypoxia. Mean arterial BP showed a peak increase (3 to 12 per cent) at 1 to 2½ min over pre-hypoxic values in only 4 animals. With a single exception mean arterial BP fell during hypoxia by a mean of 16 ± 12 per cent to a final mean arterial BP of 109 ± 15 mmHg. In 15 animals an initial peak heart rate was 22 ± 14 per cent and in 16 the rate at the end of hypoxia was still 16 ± 10 per cent above the pre-hypoxic rate. At the end of hypoxia there was a net increase in intracranial pressure of 78 ± 43 mmH_2O in 15 animals and in venous sinus pressure of 61 ± 60 mmH_2O in 16.

In final blood samples during hypoxia mean PaO_2 was 21.3±2.5 mmHg, mean $PaCO_2$ was 29.3±4.6 mmHg and mean a pH was 7.509±0.045 (n = 18). Corresponding venous sinus values were 12.6±3.7 mmHg, 32.1±5.1 mmHg and 7.479±0.039 (n = 18). The mean final value for plasma lactate was 3.26±1.27 mmol/l (n = 14) at a mean of 19 min from the start of hypoxia and PaO_2 was 20.8±2.6 mmHg. The corresponding value for plasma pyruvate was 0.162±0.079 mmol/l (n = 10).

The EEG in 8 animals showed one or more brief episodes of hypoxic activation sometimes leading to a decline to score 6 at depth (No. 16, fig. 9, sample 2) and/or epidural electrodes. This coincided with a slight decrease in inspired oxygen tension on a background of a slowly falling mean arterial BP. Simultaneous elevation of the T-wave of the ECG was evident. Slightly raising the inspired oxygen tension reversed the EEG and ECG changes.

Occlusion of Left Common Carotid Artery during Hypoxia (18 Animals, figs. 5 and 6)

As while breathing air the earliest and most marked effects of left carotid occlusion were on the mean arterial BP. There was a peak increase from a mean of 109±15 mmHg to a mean of 125±13 mmHg in 10 animals at about 1 min. Occlusion lasted for a mean of 21±4 min in 17 animals (but 12½ min in No. 5—*vide infra*) and final mean arterial BP had risen by a mean of 15±8 mmHg (that is 15±10 per cent) in 9, it had fallen by 18 and 8 mmHg in 2 and was unchanged in 6. The mean mean arterial BP just before occlusion of the right common carotid artery was 113 ± 20 mmHg (n = 17). There was neither an early peak in heart rate nor overall change; respiratory rate was slightly raised in 11 animals. In the 15 animals in which data were available there was an early rapid fall in intracranial pressure of not more than 50 mmH_2O in 7. Just before occlusion of the right common carotid artery mean intracranial pressure was 41 ± 23 mmH_2O below the level at the end of hypoxia *per se* in 11 animals and was unchanged in the other 4. The venous sinus pressure showed a net fall of 36 ± 22 mmH_2O in 11 animals.

In final blood samples during left carotid occlusion mean values were PaO_2: 21.7±2.2 mmHg, PvO_2: 11.2±2.5 mmHg, $PaCO_2$: 27.3±4.8 mmHg, $PvCO_2$: 30.3±4.7 mmHg, a pH: 7.497±0.034 (all n = 17) and v pH: 7.468±0.035 (n = 16). The rate of rise of plasma lactate was unchanged when left carotid occlusion was added to hypoxia and a level of 4.75±2.11 mmol/l (n = 14) was attained at a mean of 13 min from the start of occlusion and at a mean PaO_2 of 21.5±2.2 mmHg. Plasma pyruvate had reached a mean of 0.228±0.055 mmol/l (n = 10) at a mean of 15 min from the start of the occlusion.

Alterations in the EEG were restricted to a single animal (No. 5, Table 2) in which the EEG became isoelectric at 76 s. The mean arterial BP, heart rate and respiration then remained virtually unchanged until the artery clasp was removed at 12½ min, but the intracranial pressure and venous sinus pressure showed net rises of 80 and 30 mmH_2O, respectively. In samples taken at 11½ min PaO_2 was 23.5 mmHg, $PaCO_2$ 22.6 mmHg and a pH 7.488 and venous values were 10.4 and 26.0 mmHg and 7.416. The rapid decline in the EEG to an isoelectric state soon after the occlusion of one common carotid artery was attributed to a failure of 'cross filling' probably as a result of a major anomaly of the anterior portion of the circle of Willis which was confirmed at autopsy. Events after the release of the single artery clasp are described, together with those occurring after release of the two clasps in the other 17 animals (*vide infra*).

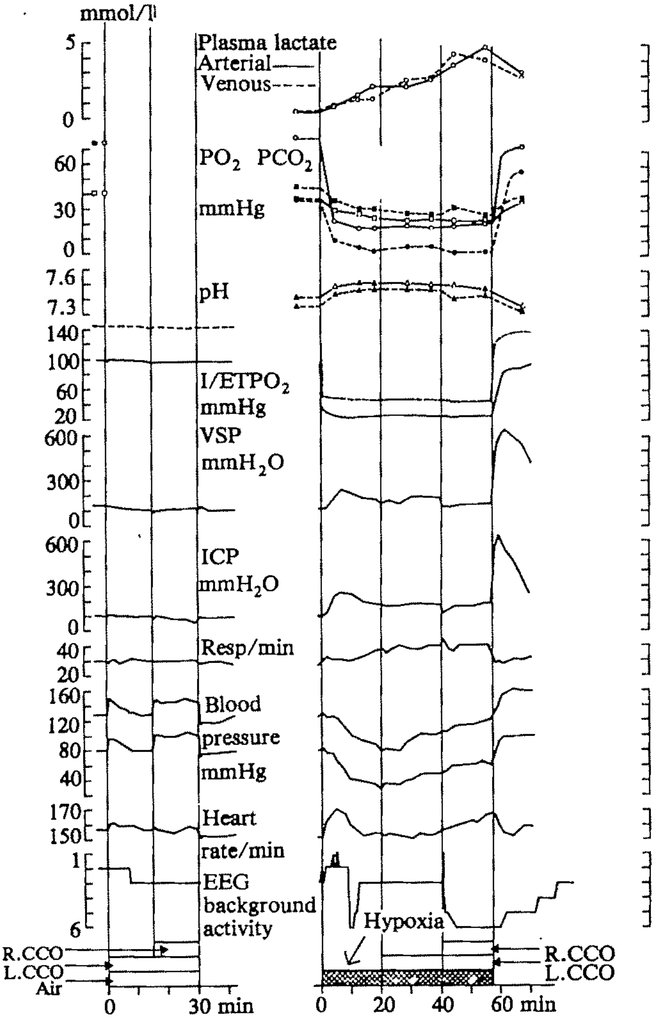

FIG. 5. *Animal No. 18. Left*, physiological consequences of sequential CCO breathing air. *Right*, physiological effects of hypoxia *per se* and of additional sequential CCO. Note transient depression of EEG during hypoxia due to 0.2 ml bolus of Althesin; also hypoxic activation at moment of right CCO. VSP = Venous sinus pressure. ICP = Intracranial pressure.

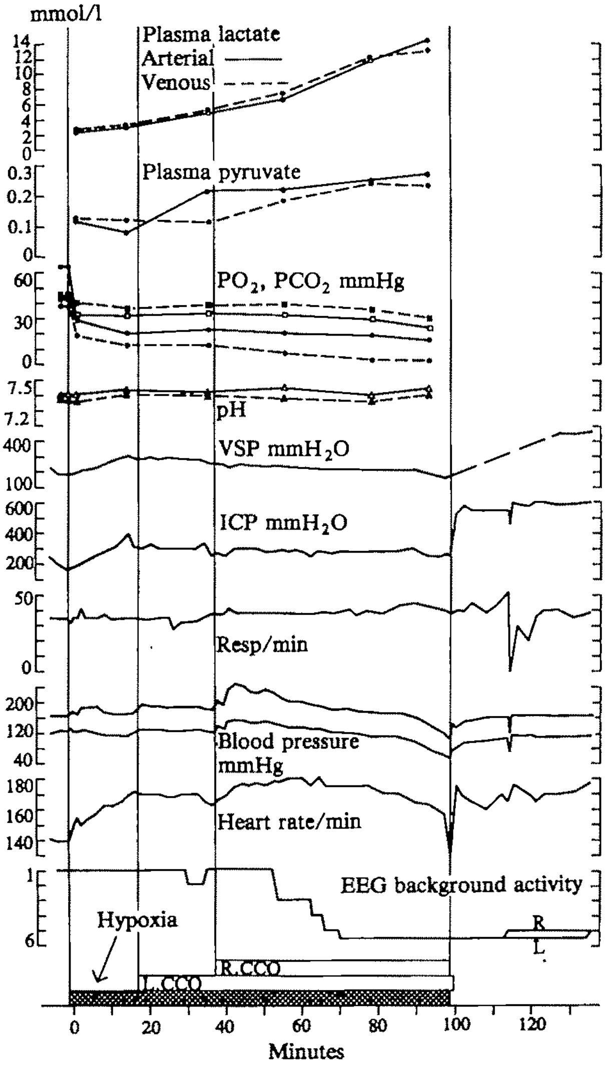

FIG. 6. *Animal No. 10.* Physiological effects of hypoxia *per se* and of additional sequential CCO.

Additional Occlusion of Right Common Carotid Artery during Hypoxia (17 Animals, figs. 5 and 6)

The duration of the additional occlusion of the right carotid artery (that is bilateral occlusion) represented the sum of the time until maximum EEG depression (score 5 or 6) was attained together with a deliberately chosen period at this EEG score. As minor brain damage occurred following 8 min of maximum EEG depression the range 6 to 15 min of such depression was explored in ½ to 1 min steps in 13 animals. In the other 4 animals the range 17 to 28 min led to brain damage that was more severe yet compatible with survival. In 15 animals the mean duration of bilateral carotid artery occlusion was 21 ± 6 min but was 62 and 69 min in the other 2 (Nos. 10 and 17, Table 2). Blood samples (1 to 4 in number according to the duration of arterial occlusion) were available in 15 of the 17 animals. The mean values ± 1 SD (n = 15) were:

PaO_2	22.1 ± 2.4 mmHg	PvO_2	7.7 ± 3.4 mmHg
$PaCO_2$	27.2 ± 5.1 mmHg	$PvCO_2$	33.2 ± 5.8 mmHg
a pH	7.481 ± 0.031	v pH	7.407 ± 0.029

The principal effects of adding occlusion of the right to that of the left common carotid artery (hypoxia unaltered) were upon the mean arterial BP and the EEG (Table 2). A mean peak mean arterial BP of 128 ± 16 mmHg occurred at a mean of 31 ± 19 s. Respiratory rate increased by 13 ± 9 per cent and early increases in heart rate were negligible. The intracranial pressure fell by 56 ± 36 mmH$_2$O in 11 animals and VSP fell by 62 ± 39 mmH$_2$O in 12, both at about 30 s. During the period of bilateral carotid artery occlusion a minor net increase in intracranial pressure occurred in only 3 animals (occlusion 24 to 70 min).

TABLE 2

	1	*2*	*3*	*4*	*5*	*6*		*7*
No.	*Time to EEG score 3*	*MABP at score 3*	*Time to EEG score 5* or 6*	*MABP at score 5 or 6*	*MABP 2 → 4*	*Peak MABP %pre-RCCO*		*Vert. basilar flow*
						Air	*Hypoxia*	
24	19 s	103	23 s	105	0	11(136)	19(98)	X
14	26 s	158	56 s	162	0	36(138)	20(132)	X
•5	24 s	114	76 s	119	+5	n/a	6(111)	X
28	26 s	123	89 s	120	0	26(167)	14(110)	X
3	15 s	88	90 s*	92	0	n/a	18(79)	X
6	25 s	100	2½ min	108	+8	n/a	21(89)	X
18	19 s	92	4 min	97	+5	14(118)	7(86)	XX
19	28 s	143	5 min	160	+17	23(136)	26(124)	X
20	42 s	129	6 min	125	0	11(143)	9(116)	XX
15	44 s	132	6½ min*	130	0	14(113)	14(121)	X
26	21 s	161	10 min	130	−31	17(150)	21(134)	X
16	3 min	117	10 min	107	−10	18(141)	9(112)	XX
9	25 s	95	12½ min	85	−10	n/a	8(88)	XXX
7	6 min	136	13½ min	141	+5	n/a	16(130)	XX
25	52 s	110	14 min*	100	−10	2(148)	3(113)	XXX
4	3 min	103	19 min	86	−17	n/a	6(100)	XXX
10	16 min	160	34 min*	138	−22	n/a	21(147)	X
17	21 min	122	44 min	85	−37	8(121)	9(120)	XXX

The 18 *Papio Anubis* arranged in order of increasing times to EEG score 5 or 6 (column 3) with mean arterial BP at that time (column 4). Also time to EEG score 3 (column 1) and mean arterial BP at that time (column 2). Column 5 = change in mean arterial BP (if 5 mmHg or more) from column 2 to column 4. Column 6: figures in brackets are levels of mean arterial BP just before right common carotid occlusion (RCCO). Column 7 = estimate of vertebrobasilar flow (X-XXX) based on preceding data. * = EEG score 5. n/a = not available. • = left carotid occlusion only.

The EEG declined to score 3 and sooner or later became isoelectric (13 animals) or nearly so. In 12 of the 17 animals hypoxic activation for up to 1 min immediately preceded the EEG decline. It did not occur in the 2 animals (Nos. 10 and 17) in which EEG decline was delayed and slow. There was considerable variability in the times at which the EEG declined to score 3 (15 s to 21 min) and to scores 5 or 6 (23 s to 44 min) in the 17 animals. Table 2 presents data for each animal concerning the time course of EEG decline and the effects of carotid occlusion on the mean arterial BP. The last column is an estimate of the adequacy of collateral blood flow (largely vertebrobasilar) based upon all the preceding data. Thus, a major increase in mean arterial BP after right common carotid occlusion during hypoxia (usually similar to that recorded while breathing air) implied a major fall in pressure in the carotid sinus, a sharp decrease in stretch receptor discharge and a corresponding sympathetic release. It also implied poor collateral flow reflected in a rapid decline of the EEG as in Nos. 3, 6, 14, 18 (fig. 5), 24 and 28. However, this decline could be delayed if a high level of mean arterial BP was maintained during hypoxia as in No. 10 (fig. 6).

As final blood samples were taken at 13 to 66 min after right carotid occlusion the range of plasma lactate was wide, that is 3.65 to 16.98 mmol/l, mean 7.88 ± 4.1 mmol/l (n = 12). During the longer periods of occlusion (for example Nos. 4, 10 and 17) the rate of lactate accumulation appeared to increase during the period when the EEG was declining to score 5 or 6. Plasma pyruvate reached a final mean of 0.308 ± 0.058 mmol/l (n = 8) at 32 ± 18 min from the start of occlusion.

From the time of attaining EEG score 3 to the release of the clasps and the end of hypoxia there were no significant alterations in heart rate, respiration, intracranial or venous sinus pressure. However, ECG showed elevation of the T-wave in 8 animals and occasional arrhythmias occurred in 12 animals.

Between the attainment of an isoelectric EEG and the release of the artery clasps the mean arterial BP rose in 7 (mean 13 ± 7 mmHg), it fell in 7 animals (mean 21 ± 21 mmHg), it was unaltered in one and comparable information was not available in Nos. 3 and 28. The lowest mean arterial BPs just before release of the clasps were 61, 70 and 72 mmHg in animals Nos. 9, 4 and 10, respectively. The mean arterial BP at the end of bilateral arterial occlusion was 113 ± 33 mmHg (n = 17).

Termination of Hypoxia with Release of Artery Clasps (18 Animals)

The precise time of simultaneous common carotid artery release was indicated by a sharp rise in intracranial pressure. A mean mean arterial BP just before simultaneous release of the clasps (fig. 7) of 124 ± 27 mmHg fell to a mean minimum of 94 ± 12 mmHg at 17 ± 4 s (all n = 13). This was followed by a rapid rise to a mean of 109 ± 11 mmHg at 1 min and to 122 ± 8 mmHg at 4 min. In a single animal (No. 4, fig. 7) the mean arterial BP fell to 50 mmHg but had risen to 103 mmHg at 2 min. In No. 9 the mean arterial BP was 61 mmHg just before clasp release but fell no further after release as mechanical ventilation was required for less than 1 min during which the mean arterial BP rose rapidly to just over 100 mmHg. Heart rate fell from a mean of 187 ± 14/min to a mean minimum of 158 ± 20/min at 5 ± 2 min after release of the clasps. It then rose progressively and often exceeded control values. Elevation of the T-wave and cardiac arrhythmias, if present, disappeared a few seconds after release. Respiratory rate had returned to normal at about 1 min.

After carotid release a mean peak intracranial pressure of 236 ± 101 mmH$_2$O above that at the end of arterial occlusion was attained at 115 ± 48 s (fig. 8, n = 13, since carotid occlusion unilateral in No. 5, release not simultaneous in Nos. 3, 9 and 10 and a period of mechanical ventilation with air in Nos. 9 and 28). There were similar increases in venous sinus pressure. The individual rises in intracranial pressure after carotid release varied widely as did the times until intracranial pressure had fallen to an arbitrary value of 50 mmH$_2$O above that obtaining just before the end of occlusion. It is to be noted that in Nos. 14, 15 and 25 (normal brains) these times were 2 to 13 min (compared with a mean time of 72 ± 59 s to the pre-occlusion level after release of both artery clasps while breathing air). In Nos. 4 and 10 brain damage was severe and the intracranial pressure was still considerably elevated at 2 to 3 h but showing a uniform slow decline. With four exceptions increases in venous sinus pressure were up to 150 mmH$_2$O more than the corresponding increases in intracranial pressure. In No. 5 the intracranial pressure rose by 170 mmH$_2$O 15 s after release of the left carotid artery.

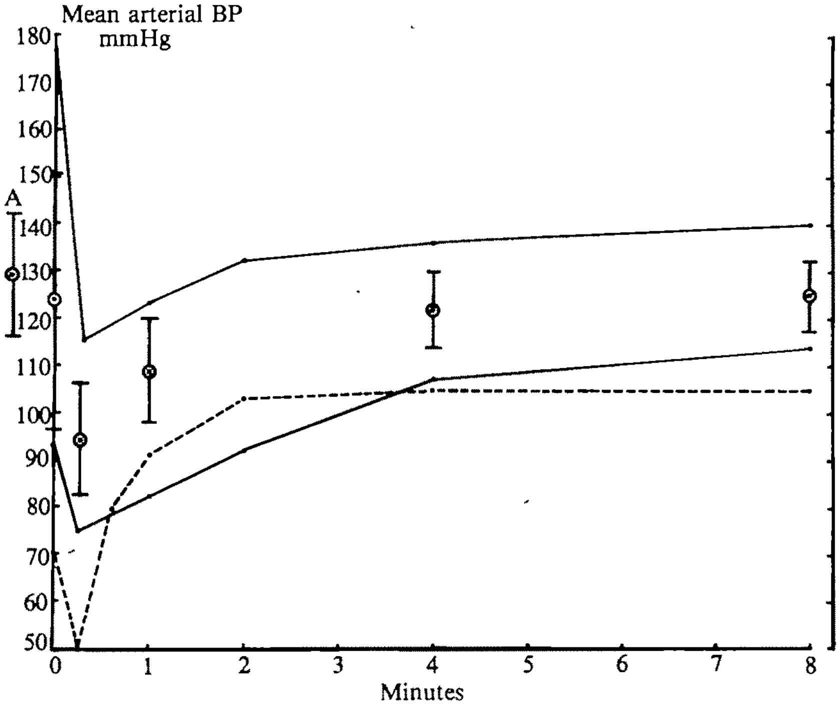

FIG. 7. MABP (mean ± 1 SD and range) at 0 min, minimum at 17 ± 4 s, and at 1, 4 and 8 min after release of artery clasps with resumption of air breathing (n = 13). A = pre-hypoxic MABP (n = 15). Dotted line = exceptional course of MABP in animal No. 4.

The pupils were up to two-thirds dilated (right more than left in 3) at the end of carotid occlusion and after release they returned to normal at 1½ to 4 min, but not until at least 10 min in 3 animals (with severe brain damage). In animal No. 4 also with severe brain damage the pupils were normal at 2½ min.

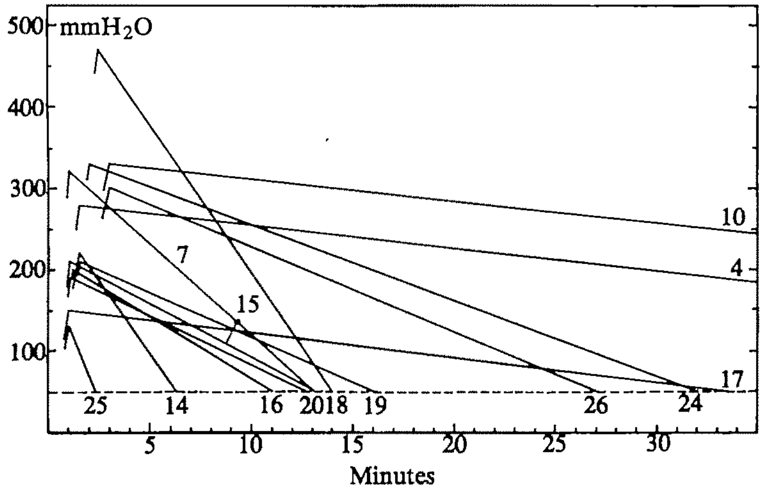

FIG. 8. Times (13 animals with individual numbers) from release of artery clasps and end of hypoxia to peak intracranial pressure and to return to an arbitrary 50 mmH_2O above the level at the end of bilateral CCO (depicted as 0 mmH_2O) except in animals Nos. 4 and 10.

The EEG was isoelectric or nearly so for 6 to 62 min (Table 3). For each animal this period comprised:

(i) the chosen interval between attainment of this state and clasp release (range 6 to 28 min, mean 14 ± 6 min), and

(ii) the interval from clasp release until the return of some activity (range 0 to 34 min, mean 6 ± 8 min).

The returning activity generally took the form of low voltage rhythmic spindles at 7 to 14 Hz (score 5) maximal in the Rolandic areas. Recovery to score 4 occurred at a mean of 17 ± 15 min from removal of the clasps. Asymmetry of returning activity, that over the right hemisphere recovering earlier, was present in 8 animals. Abnormal features such as focal spikes and sharp waves, repetitive diphasic transients, persistent delta activity or local flattening were noted in 6 animals all with brain damage. The mean total score (visual assessment) for the period of EEG depression was 212 ± 107 (n = 18); that derived from computer analysis was 236 ± 130 (n = 14). In 2 animals (No. 16, fig. 9 and No. 20) the total computer scores from the depth electrodes were 7 per cent higher (that is greater EEG depression) than the corresponding scores from the overlying convexity electrodes.

Neurological State (Table 3)

On the morning following the experiment 9 animals were conscious, active, eating and drinking normally and exhibited no neurological abnormality. Five (Nos. 3, 7, 9, 17 and 20), while conscious, showed largely right-sided impairment. When seated there were side-to-side flailing movements of the flexed right leg. The right arm was extended with the wrist flexed. There was additional increase in muscle tone in the left limbs of one animal, deviation of the right eye to the right in another and deviation of both eyes and the head to the right in a third.

Four animals were unconscious. One (No. 6) was *in extremis* with flailing limbs and slowing respiration and perfusion-fixation was carried out without delay. In one (No. 24) there was head retraction and increased tone in limb muscles (R > L). When Althesin anæsthesia lightened, myoclonus of limb muscles appeared. In the other 2 animals (Nos. 4 and 10) rhythmic myoclonus, extension spasms and concurrent pupillary dilatation were obvious and there was quadriparesis (R > L).

TABLE 3

	1			*2*	*3*	*4*		*5*		*6*	*7*	*8*	
	Path. score					*EEG score 5* or 6 (min)*						*Follow up*	
No.	*Total*	*L*	*R*	*BCCO (min)*	*Final MABP*	*During BCCO*	*Total*	*EEG score 4 or > 4* *L*	*R*	*EEG comp score* *L*	*ICP rec. time (min)*	*EEG*	*Neurol*
14	0	0	0	10	177	9½	13	121	114	124	6¼	0	0
15	0	0	0	26	139	6*	6	144	144	175	13	0	0
25	0	0	0	24	98	10*	11	124	124	114	2	0	0
16	1	1	0	25	97	15	17	120	107	149	11	0	0
18	4	3	1	17	102	12	13½	188	186	218	14	0	0
19	4	3	1	14	148	9	10	112	112	131	16	0	0
28	6	4	2	15	n/a	16	16	159	159	n/a	n/a	0	0
7	8	5	3	24	135	10¼	17½	162	160	163	13	+	+ +
20	8	4	4	20	136	14	15	185	185	194	12½	+	+ +
26	8	4	4	23	157	13	13½	207	207	n/a	27	0	0
9	10	5	5	23	61	11	18	228	215	205	n/a	+	+ +
$^{\emptyset}$5	13	9	4	12½	116	12½	15	187	134	n/a	28	+	0
3	18	10	8	9	n/a	8*	15	148	148	n/a	n/a	+	+ +
6	20	11	9	24	96	23	38	277	249	267	n/a	n/a	+ + +
17	21	14	7	70	96	26	28½	355	355	390	34	+ +	+ +
24	21	10	11	17½	117	17	20	221	221	221	32	+ + +	+ + +
4	28	14	14	27½	70	10	20	351	351	388	> 58	+ + +	+ + +
10	33	18	15	62½	72	28*	62	528	507	575	> 75	+ + +	+ + +

The 18 *Papio Anubis* arranged in order of increasing total brain damage scores (column 1). Duration of bilateral common carotid occlusion (column 2), mean arterial BP just before release of clasps (column 3), duration of EEG score 5 or 6 during bilateral common carotid occlusion and total including recovery period (column 4), EEG scores total (during bilateral common carotid occlusion and recovery period), left and right—visual (column 5) and computer, left (column 6) Column 7 = time until intracranial pressure had fallen to an arbitrary 50 mmH_2O above level at end of bilateral common carotid occlusion Column 8 = follow-up EEG and neurological status on four-point scales. * = EEG score 5. n/a = not available. $^{\emptyset}$ = left carotid occlusion only.

Follow-up EEG (Table 3)

Follow-up EEG examinations were normal in 8 animals. Mild abnormalities were present in 5 animals (Nos. 3, 5, 7, 9 and 20) and consisted of relative reduction in voltage and amount of activity, more marked over the left hemisphere or both parieto-occipital regions. More marked abnormality in No. 17 comprised asymmetrical dominant slow-wave activity (L > R) combined with intermittent left-sided spikes and reduction of spindles. Three animals showed very severe abnormalities. In No. 24 dominant slow-waves and asymmetrical spikes were replaced by repetitive, generalized or asynchronous bilateral discharges of groups of spikes often accompanied by myoclonic jerks as anæsthesia lightened. In Nos. 4 and 10 (no anæsthesia) high voltage, regularly repetitive discharges of groups of 6 to 10/s spikes, lasting ½ to ¾ s, occurred every 2 to 3 s (fig. 10). These were separated by isoelectric periods and there were occasional superimposed, left-sided, sub-clinical seizure discharges. Myoclonic jerks or decerebrate spasms with pupillary dilatation occurred at the end of each discharge. With deepening Nembutal anæsthesia for perfusion-fixation these clinical accompaniments and then the discharges gradually decreased to leave a near isoelectric tracing. No EEG was performed in No. 6.

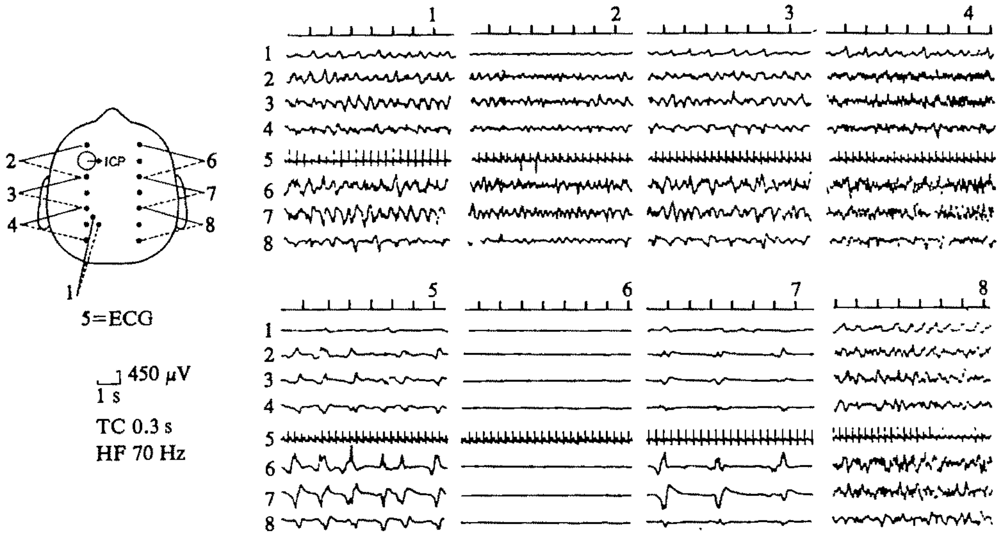

FIG. 9. *Animal No. 16.* EEG (depth recording channel 1). Samples 1, pre-exposure; 2, 12 min of hypoxia; 3, 19 min of additional left CCO; 4, 20 s of bilateral CCO during hypoxia; 5, hypoxia and bilateral CCO for 5 min; 6, the same after 25 min; 7, 9 min after release of carotids and end of hypoxia; 8, 38 min after same events. Time constant = 0.3 s. HF cut 30 per cent above 70 Hz.

Neuropathology

Macroscopic appearances. The range of brain weights was 112 to 180 g. Brain swelling was indicated in 12 by herniation of the inferior cerebellar vermis into the cisterna magna of all and additional flattening of gyri in the parietal and occipital regions of 4.

In animal No. 5 the right common carotid artery was just over half the diameter of the left and the right internal carotid made no contribution to the unpaired supracallosal anterior cerebral artery which was derived entirely from the left internal carotid artery. The posterior communicating arteries could not be identified in No. 28 and were thread-like in No. 26.

In coronal slices there was narrowing of the third and lateral ventricles of 3 brains. Some patchy discolouration of the cortex around the intraparietal sulci (L > R) was seen in 6 brains and could be traced anteriorly in a paramedian position for a variable distance.

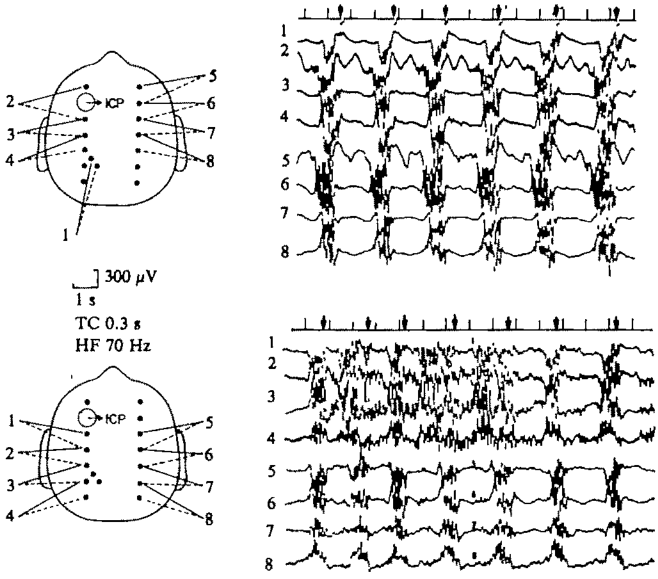

Fig. 10. *Animal No. 10.* Two samples of follow-up EEG at 15½ h (depth recording is channel 1 in upper sample). Arrows indicate timing of myoclonic jerks. Time constant = 0.3 s. HF cut 30 per cent above 70 Hz.

Microscopic appearances. The only neuronal alterations observed were some stages of ischæmic cell change. Damage was restricted to portions of the arterial boundary zones in the cerebral cortex, and to the caudate nucleus, putamen and globus pallidus. Asymmetry of damage was frequent and the damage scores (totals) for each hemisphere are given separately (Table 3).

The range of survival times was 15 to 46 h so that the earlier stages (microvacuolation and ischæmic cell change (Brown and Brierley, 1968)) of the ischæmic process were not seen. Ischæmic cell change with incrustations was seen in large cortical pyramidal cells when survival was not more than 24 h. The commonest stage was that of homogenizing cell change in which a shrunken, dark-staining nucleus was surrounded by variably reduced cytoplasm staining pink with eosin and mauve with Luxol-fast blue. Even at 15 h small cells in the caudate nucleus and putamen were reduced to shrunken naked nuclei.

Necrosis of white matter was never observed and there was only slight pallor of myelin staining subjacent to major ACA/MCA boundary zone lesions in 3 animals.

The distribution of ischæmic damage. The brains of Nos. 14, 15 and 25 were normal. Minimal damage was seen as a few ischæmic neurons in the floor of the left intraparietal sulcus (No. 16, figs. 1 and 9). Moderate damage involved more of the posterior to anterior extent of the ACA/MCA boundary zone and when it reached the central sulci minimal damage was also seen around the intraparietal sulcus on the right side (Nos. 18 and 19). The maximal damage was always at the junction of the three boundary zones in the intraparietal sulcus.

There was minor damage (grade 1) in the basal ganglia of Nos. 7, 26 and 28 (L > R) with involvement of the outer segment of the globus pallidus in No. 26. Boundary zone damage increased from No. 20 to No. 6 (Table 3) but there was none in the basal ganglia. No. 5 showed a marked excess of damage along the left ACA/MCA boundary zone and was the animal in which no ACA arose from the right internal carotid artery. In the next 2 animals (Nos. 3 and 6) damage was greater along the boundary zones and No. 6 was the only instance of additional MCA/PCA boundary zone involvement, yet the basal ganglia were spared in both.

In the last 4 animals ischæmic damage was marked in the ACA/MCA boundary zones and the basal ganglia were involved in all. In No. 17 the body of the caudate nucleus (score 2 L, 1 R) and the outer segment of the right globus pallidus (1) were involved. In No. 24 damage was seen in each putamen (1 L, 2 R) and in the head of each caudate nucleus (1 L and R). In No. 4 only the outer segment of each globus pallidus was involved (3 L and R). In No. 10 (fig. 11) damage was minor in each putamen (1 L and R) and in the head of each caudate nucleus (1 L and R). It was moderate in the body of each caudate nucleus (2 L and R) and major in the outer segment of each globus pallidus (3 L and R).

The Correlates of Brain Damage (*Table 3*)

In addition to providing general physiological data before, during and after combined hypoxia and carotid occlusion the study has provided independent quantification of the following: the total EEG score (separate visual and computer assessments), intracranial pressure recovery time and brain damage scores. When the data in columns 2 and 4 were plotted against the brain damage scores no linear relationships were found although the longest periods of arterial occlusion and of isoelectric EEG tended to be associated with more severe brain damage.

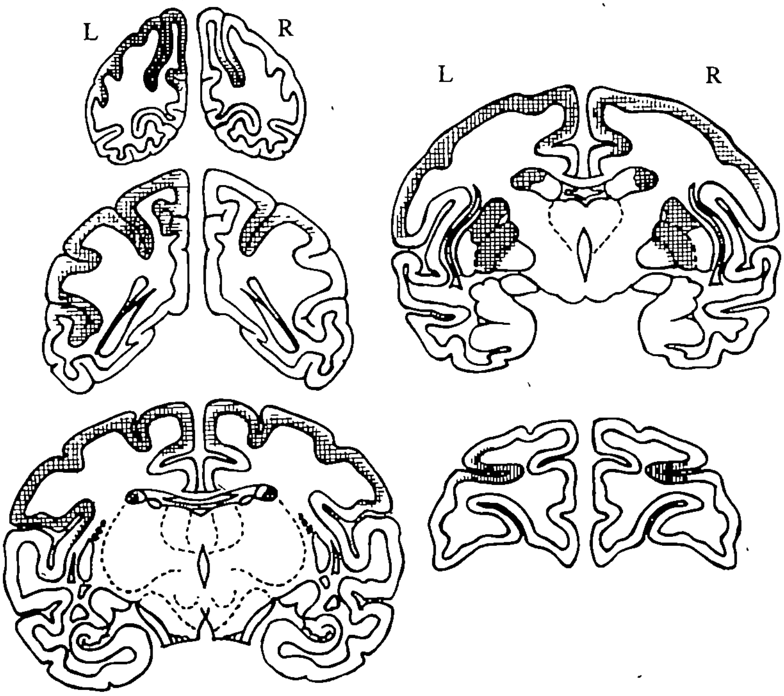

FIG. 11. *Animal No. 10.* Survival 16 h. Distribution of ischæmic damage (indicated by intensity of shading) in the cerebrum at five standard coronal planes.

The follow-up EEG and neurological examinations were normal in the 3 animals with normal brains. They were also normal in 5 of the animals with mild damage (Nos. 16, 18, 19, 26 and 28), but in the remainder they provided a reasonable index of the severity of brain damage.

A better and earlier index of the presence and extent of brain damage was provided by the total EEG scores (score 4 or > 4, assessed visually and by computer (fig. 12)) and, unexpectedly, by the duration of raised intracranial pressure after carotid release (fig. 13).

Correlation coefficients between the total EEG scores (4 or > 4) for left and right sides were calculated. The score for the left was significantly greater than that for the right (Student's t test, $t = 2.33$; $P < 0.05$). Similar coefficients for brain damage scores showed an even more significant excess of left over right ($t = 3.36$; $P < 0.01$).

DISCUSSION

In order to define the physiological basis for ischæmic damage along the arterial boundary zones of the primate forebrain a degree of hypoxia was selected that permitted the retention of spontaneous respiration. Cerebral blood flow was reduced without jeopardizing cardiac function by the sequential occlusion of the

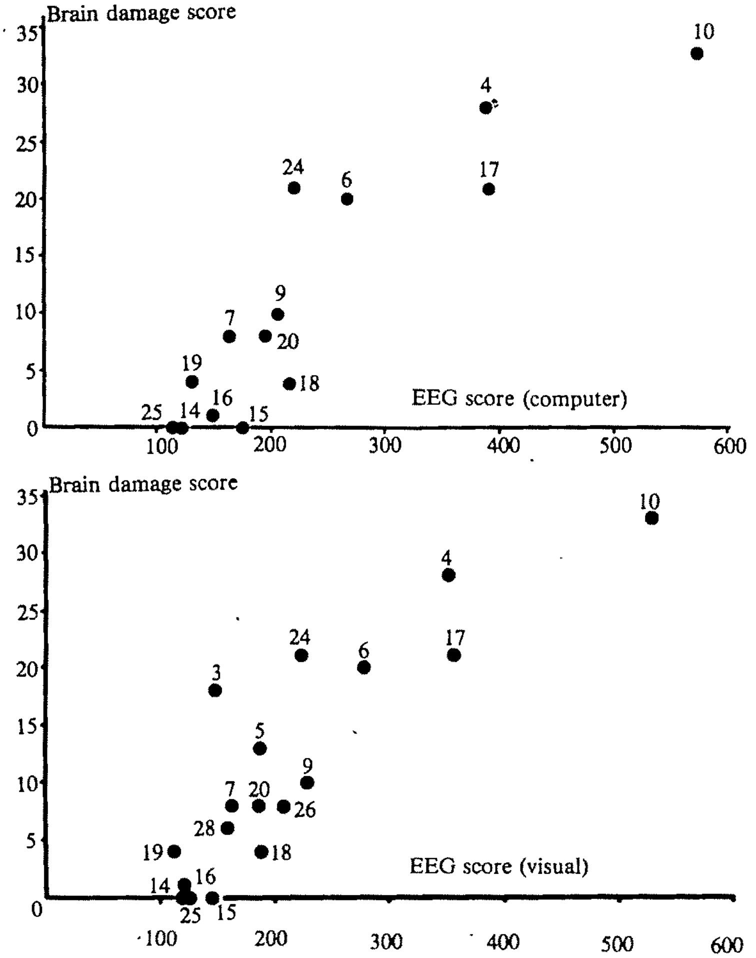

FIG. 12. Brain damage scores *v* EEG scores (left parietal epidural recordings): computer, n = 14 and visual, n = 18.

common carotid arteries. After the animals were returned to their cages there was no therapeutic intervention and within an elective survival period of 48 h assessment of brain function could be carried out before fixation of the brain by *in vivo* perfusion as a preliminary to systematic neuropathological examination.

In the paralysed and mechanically ventilated rat with a PaO_2 of 21 mmHg and a mean arterial BP of at least 120 mmHg occlusion of a single common carotid artery resulted in brain damage (Salford, Plum and Brierley, 1973). This consisted of ischæmic neuronal alterations within the territory of the ipsilateral MCA and only minor damage along the two related arterial boundary zones. In the baboons of this study, however, it was necessary to add bilateral common carotid occlusion to the hypoxia represented by a PaO_2 of 21 to 24 mmHg in order to produce brain damage.

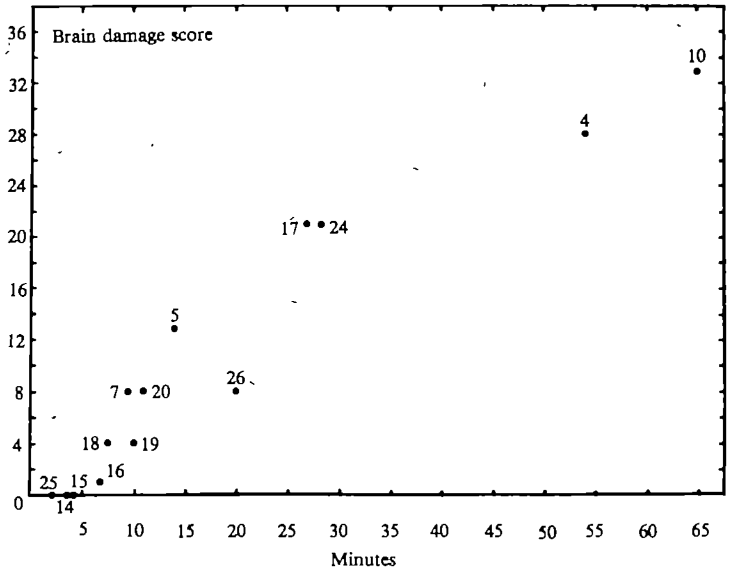

FIG. 13. Brain damage scores v times for intracranial pressure to fall to half the difference between peak values just after and values just before the end of carotid occlusion with hypoxia.

Within the cerebral cortex this was restricted to the arterial boundary zones and the central MCA territory was never involved. A similar restriction of cortical damage to the boundary zones has not been described in the Levine preparation in the rat (Brown and Brierley, 1968; Salford *et al.*, 1973; Levy, Brierley and Plum, 1975).

Thus, the essential differences between the species are that with a PaO_2 of 21 to 24 mmHg cortical damage in the mechanically ventilated rat follows occlusion of a single common carotid artery and lies within the MCA territory while in the spontaneously breathing baboon damage only occurs after occlusion of both common carotid arteries and is confined to the arterial boundary zones. Further, ischæmic damage is variable in the basal ganglia of each species, always absent in the hippocampus of the baboon but major and almost invariable in that of the rat.

At a PaO_2 of 21 to 24 mmHg cerebral vasodilatation will be maximal (that is, autoregulation of flow is in abeyance) so that compensation for occlusion of a major artery will depend solely on the volume flow available from collateral sources. In the rat model it has been shown that this level of PaO_2 produces a 4- to 6-fold increase in blood flow in the MCA territories. This was reduced to a 2-fold increase in the ipsilateral cortex after occlusion of the common carotid artery (Salford and Siesjö, 1974). This relative ischæmia must imply the inability of cross-filling together with vertebrobasilar flow to compensate for occlusion of one common carotid artery. In the baboon, on the other hand, unilateral common carotid occlusion during hypoxia did not affect the EEG suggesting that this was maintained by cross-filling and some contribution from vertebrobasilar flow. After occlusion of the second artery in the baboon the principal source of collateral blood flow is the vertebrobasilar system *via* the posterior communicating arteries. Some reversal of flow in the external carotid arteries through their anastomoses with branches of the aorta in the neck cannot be excluded nor can it be assessed.

It was evident that, in the baboon, bilateral common carotid artery occlusion for up to 62½ min (during hypoxia) reduced blood flow to a critical level only locally (i.e. along the arterial boundary zones) while the central regions irrigated by the three major cerebral arteries were always spared. In only 2 animals, Nos. 4 and 10 (fig. 11), did damage spread appreciably outside (i.e. in the coronal plane) the line of the ACA/MCA boundary zones and particularly in the parieto-occipital regions. The retention of a normal EEG after unilateral common carotid artery occlusion and the restriction of damage to the cortical boundary zones after bilateral carotid occlusion in the baboon suggests that the evolution of the primate neocortex has been accompanied by an increase in the anastomotic capacity of the circle of Willis.

A reasonable index of the adequacy of blood flow from all sources after common carotid artery occlusion was provided by the associated increases in mean arterial BP during spontaneous air breathing. The range 23 s to 44 min for the attainment of an isoelectric EEG after occlusion of the second common carotid artery (Table 2) indicates the wide variation in inflow from collateral sources and from the vertebrobasilar system in particular. The occlusion of one artery permitted assessment of cross-filling and occlusion of the second artery provided comparable information concerning the vertebrobasilar contribution. A large rise in mean arterial BP occurring almost immediately after occlusion of the second common carotid artery implied a major fall of blood pressure within the sinus lumen. This in turn implied a very limited inflow *via* the posterior communicating arteries. The latter were either absent or thread-like in the 2 animals (Nos. 26 and 28) in which there were very marked rises in mean arterial BP after bilateral carotid occlusion.

In man, transient occlusion of one common carotid artery (local anæsthesia) led to increases in mean systemic blood pressure of 0 to 64 mmHg (Moore and Hall, 1969). The highest recorded blood pressure was 280/120 mmHg and systolic pressure was 200 mmHg or more in 21 of 43 cases. As pressure was also measured above the occlusion it was concluded that '... when internal carotid back pressure is compared to the rise in mean arterial BP following carotid clamping there appears to be a reciprocal relationship with a correlation coefficient of 0.45 which is statistically significant'. The range of internal carotid 'back pressure', i.e. distal to the occlusion, was 12 to 88 mmHg and consciousness was lost if this pressure fell below 22 mmHg.

The peak values for blood pressure in the above study in man and in the baboons of the present series are notable for two reasons. Firstly, in the present study, a rise in mean arterial BP to a mean of 148 ± 19 mmHg after occlusion of one common carotid artery while breathing air was unaccompanied by evidence of increased cerebral blood flow. Thus, there were no increases in intracranial and venous sinus pressure such as occurred early in the subsequent period of profound hypoxæmia and were so marked during the 'luxury perfusion' immediately following release of both arteries and the resumption of air breathing. Secondly, and in sharp contrast, the corresponding increases in blood pressure are minor and transient when sequential common carotid occlusion is carried out in paralysed and mechanically ventilated baboons with mean control mean arterial BP in the range 81 ± 9 to 102 ± 7 mmHg (Jennett, Miller and Harper, 1976).

In studies in the baboon of the effects of hypertension (Strandgaard, Mackenzie, Jones and Harper, 1976) in which the upper limit of autoregulation in 8 animals was at a mean arterial BP of 130 mmHg the mean control mean arterial BP was 103 ± 2 (range 100 to 109) mmHg. In contrast, the mean control mean arterial BP in the animals of the present study was 133 ± 13 (range 106 to 148) mmHg. In the animals of Strandgaard *et al.* (1976) and of Jennett *et al.* (1976) the combination of mechanical ventilation and muscular paralysis (suxamethonium chloride) was most probably responsible for the low levels of control mean arterial BP by raising intrathoracic pressure and reducing venous return. Further, Cox and Bagshaw (1979) have demonstrated in the spontaneously breathing dog that the initial level of mean arterial BP has a significant effect on the magnitude of the pressor response to bilateral common carotid artery occlusion. Thus, a larger increase in mean arterial BP is associated with a higher pre-occlusive level.

Exposure to hypoxia produced a transient hyperventilation and the mean arterial BP fell (with one exception) by a mean of 16 per cent to a final mean of 109 mmHg. As the mean PaO_2 was 21.2 mmHg at 5 min, autoregulation of cerebral blood flow would have been in abeyance from thereon. When PaO_2 is less than 30 mmHg 2- to 6-fold increases in cerebral blood flow have been described (Häggendal and Johansson, 1965; McDowall, 1966; Kogure, Scheinberg, Fujishima, Busto and Reinmuth, 1970; Berntman, Carlsson and Siesjö, 1979). In the present animals a mean increase in intracranial pressure of 78 mmH_2O (i.e. 6 mmHg) was the only available indication of increased cerebral blood flow during hypoxia.

After occlusion of the left common carotid artery during hypoxia an initial peak in mean arterial BP was either absent or less than that while breathing air. During the 20 min of left common carotid artery occlusion the downward trend of mean arterial BP during hypoxia *per se* was arrested or reversed in all but 2 animals. In spite of this, intracranial pressure had eventually fallen by a mean of 41 mmH_2O in 11 animals and was unchanged in 3. This suggests that the presumed increase in cerebral blood flow during hypoxia was partially reduced by occlusion of one common carotid artery.

Just *before* additional occlusion of the right common carotid artery the mean arterial BP was generally lower than the comparable value when breathing air. Just *after* right common carotid occlusion there was a peak mean arterial BP in all 17 animals. These peaks in comparison with those during air breathing (Table 2) were smaller in 4 (Nos. 14, 16, 18 and 28), equal or nearly so in 5 (Nos. 15, 17, 19, 20 and 25) and greater in 2 (Nos. 24 and 26) animals (comparable information being unavailable in 7). Two-thirds of the rise in mean arterial BP after bilateral common carotid occlusion in the conscious dog can be attributed to increased total peripheral resistance (Kirchheim, 1976). The lesser increases in mean arterial BP after bilateral carotid occlusion during hypoxia in 4 baboons might be due to a diminished vasoconstrictor response in a widely dilated vascular bed. However, as the increases in mean arterial BP during occlusion with hypoxia were equal to these recorded while breathing air in 5 animals and were, in fact, greater during hypoxia in 2, it is probable that differences in the sinus reflex response to carotid occlusion may lie at a central rather than at a peripheral level, that is in the nucleus of the tractus solitarius or in the reticular formation.

Table 2 shows the general tendency for an early attainment of EEG scores 5 or 6 to be associated with a poor vertebrobasilar inflow and late attainment of such scores with a good inflow. However, although the heights of the mean arterial BP peaks during air breathing enabled an estimate to be made of the likely extent of the vertebrobasilar contribution, such conclusions were only of value in predicting the time to maximum EEG depression when there was a comparable level of mean arterial BP. Thus, a higher mean arterial BP could compensate for a vertebrobasilar inflow estimated as poor and lead to a delayed failure of the EEG (No. 26). On the other hand, a low mean arterial BP could lead to early EEG silence in spite of a vertebrobasilar contribution originally estimated as good (No. 18). EEG silence was attained at 23 s to 6½ min from the start of bilateral carotid occlusion in the first 10 animals of Table 2 and during these periods mean arterial BP was either unchanged or even rising. As flow would have been pressure-dependent no additional decrease in forebrain blood flow can be implicated in the decline of the EEG from score 3 to the isoelectric state. Between this point and release of the clasps the mean arterial BP rose in all but 2 animals. As the times to attainment of an EEG score of 5 or 6 increased progressively in the remaining 8 animals to 44 min in No. 17 it can be seen (Table 2) that a vertebrobasilar inflow assessed as moderate or good was the principal factor in the maintenance of an adequate oxygen supply to the forebrain. The failure of this supply, reflected in the attainment of EEG silence, was in most of these 8 animals due to an appreciable fall in mean arterial BP in the interval between an EEG score of 3 and electrical silence.

In these 8 animals, because the rate of decline of the EEG was slow, it was observed, incidentally, that the decline at the depth electrode could be accelerated or even reversed by a minor decrease or increase in the proportion of oxygen in the inspired gas mixture. As these manœuvres had no observed effects on any of the recorded variables other than the EEG the conclusion was inescapable that the local EEG failure was due to a simple local inadequacy of oxygen supply. The reversibility of the isoelectric EEG at the confluence of the arterial boundary zones by minor manipulation of PIO_2 without effects on systemic circulation implies that there can have been no local circulatory arrest at that time. Also the latter could not have occurred during the remainder of the period of bilateral carotid occlusion as the mean arterial BP just before release was in the range 96 to 177 mmHg in the first 10 animals of Table 2. In 5 of the remaining 8 animals the corresponding mean arterial BP was in the range 96 to 157 mmHg but was 70, 61 and 72 mmHg in Nos. 4, 9 and 10. These low levels may have produced an additional reduction in hemispheric flow (exaggerated at the boundary zones) during the latter parts of the isoelectric periods).

In the animals of the present study arterial pH was not significantly reduced as a consequence of the high plasma lactate levels. This was due largely to the hypocapnia resulting from hypoxic hyperventilation and also to the additional buffering capacity provided by the considerably desaturated hæmoglobin. The high levels of circulating lactate must be regarded as the effects of systemic hypoxia and the study provides no convincing evidence of an additional cerebral contribution, i.e. no significant increase in V-A plasma lactate difference.

A light level (EEG score 1 to 2) of anæsthesia throughout hypoxia and sequential common carotid occlusion was maintained by the intravenous infusion of Althesin. As cerebral vasodilatation would have been maximal during this period the vasoconstriction attributed to Althesin in the normoxæmic baboon by Fitch, McGeorge and Mackenzie (1978) could not have occurred. An additional reduction in $CMRO_2$ of about one-third reported by the same workers, if present, was without effect on the EEG which remained at scores of 1 or 2. Thus, the present study can neither confirm nor exclude a possible reduction in $CMRO_2$ by Althesin. Regrettably, evidence on this point from cerebral A-V oxygen content differences is not available because of a non-systematic fault in the oximeter used to measure hæmoglobin content and oxygen saturation in all arterial and cerebral venous sinus blood samples. It can only be noted that in *Macaca Mulatta* control cerebral A-V oxygen content differences were the same under Althesin as under pentobarbitone (Brierley *et al.*, 1978). Further, the reductions in mean arterial BP and intracranial pressure that follow single injections of Althesin in the baboon (Pickerodt, McDowall, Coroneos and Keaney, 1972) did not occur when it was given by intravenous infusion. Thus, a decrease in cerebral blood flow as a direct effect of Althesin is unlikely in the animals of the present study.

After removal of the artery clasps and with the resumption of air breathing the sharp fall in mean arterial BP (figs. 5, 6 and 7), lasting for a mean of only 17 s, was due to an abrupt increase in carotid sinus stretch receptor discharge. Mean arterial BP then rose rapidly so that at 1 min after carotid release the mean was 109 mmHg and at 4 min was only slightly less than the pre-hypoxic level. Thus, significant hypotension did not occur, but in No. 4 (fig. 7) the mean arterial BP fell briefly to 50 mmHg.

The abrupt restoration of carotid blood flow into a fully dilated cerebrovascular bed produced an immediate hyperæmia ('luxury perfusion') indicated by marked increases in intracranial and venous sinus pressure (figs. 5 and 6). The former was an index of increased brain blood volume while the latter implied that for a matter of seconds and often of minutes the increase in cerebral blood flow exceeded the capacity of the non-distensible superior longitudinal sinus from which pressure was being recorded. EEG activity had returned within 3½ min after carotid artery release in those animals with normal or minimally damaged brains.

In the 3 animals with normal brains (Nos. 14, 15 and 25) intracranial pressure had fallen to the arbitrary level of 50 mmH_2O above that at the end of occlusion during hypoxia (fig. 8) after 2 to 13 min compared with a corresponding mean of 72 s after the end of occlusion while breathing air. This longer period implies that profound hypoxia delays the return of normal cerebrovascular tone and thereby the recovery of the autoregulation of cerebral blood flow. In the animals with brain damage increasing delays in the return of intracranial pressure to a near normal level were associated with increasing brain damage scores. Because the mean arterial BP rose steadily during the recovery period (fig. 7) cerebral blood flow, still being pressure-dependent, would have increased correspondingly. The only factor that might have contributed to some reduction in cerebral perfusion pressure after the animals had been returned to their cages would have been a second but unknown rise in intracranial pressure. This might have occurred in animals Nos. 4 and 10 in which intracranial pressure was still elevated at 1½ and 3½ h, respectively, and there was marked brain swelling. A similar possibility exists in No. 6 but the intracranial pressure was not recorded. Thus, a phase of slowly decreasing cerebral blood volume (due to a gradual resumption of normal vascular tone) must have been followed by one of increased vascular permeability. Yet the rates of fall of intracranial pressure were unaltered during the periods of recording. It must be borne in mind that the hind-brain was only exposed to hypoxia, it was always undamaged and, therefore, never œdematous. Thus, its normality would increase the compliance of the cranial cavity and ameliorate the effects of swelling of the cerebral hemispheres.

In 10 animals the brain damage score in the left hemisphere was greater than that in the right whilst there was a less frequent difference in EEG scores (Table 3). Neurological deficit was always more marked in the right limbs and follow-up EEGs showed a left-sided accentuation of abnormality (fig. 10). As the brains of 3 animals (Nos. 14, 15 and 25) were normal it must be concluded that the initial 20 min of unilateral common carotid occlusion during hypoxia *per se* did not lead to irreversible alterations in brain structure. However, the asymmetry of damage when bilateral succeeded unilateral common carotid occlusion can only imply that during the latter some metabolic process was initiated in the ipsilateral cerebral hemisphere which increased its vulnerability to the further reduction in forebrain blood flow when the second artery was occluded. In the present study, cerebral blood flow was not measured at either overall or regional levels. Nevertheless, some relative or absolute reduction in hemispheric flow during occlusion of the left common carotid artery must have triggered the postulated metabolic process in that hemisphere. The precise nature of this process cannot be inferred from the data of the present study and could only be defined if it were possible to measure regional cerebral blood flow and all other relevant physiological and biochemical variables in a spontaneously breathing primate with a capacity for survival.

It was apparent (Table 3) that neither the duration of bilateral carotid occlusion nor of an isoelectric EEG (during carotid occlusion or *in toto*) showed any precise relationship to the severity of brain damage. This is in agreement with the conclusion of Steen, Michenfelder and Milde (1979) that neither the fact nor the time of return of electrical activity provided an accurate index of overall neurological recovery following incomplete cerebral ischæmia in their own and other studies. However, when the EEG was assessed so as also to include the initial recovery period, the scores so derived (whether visually or by computer) showed a close correlation with the brain damage scores (fig. 12). The similar correlation of both the visual assessment and the independent computer analysis of the EEG with the neuropathological score provides validation of each as a predictor of the degree of brain damage.

A very similar relationship was demonstrable between intracranial pressure recovery times and brain damage scores (fig. 13). Thus, the EEG and intracranial pressure, each recorded during carotid artery occlusion *and* the immediate recovery period, permitted a more accurate prediction of the presence and severity of brain damage than the follow-up EEGs or neurological examination (at 14 to 46 h). Neither of the latter indicated the existence of minor degrees of brain damage subsequently proven in 5 animals, although in the other 10 more severe degrees of damage were correctly predicted. Comparable minor damage in the same arterial boundary zones was also not revealed by behavioural testing in animals subjected to sub-atmospheric decompression (Blagbrough, Brierley and Nicholson, 1973).

The regularly repetitive myoclonic jerks and extension spasms that occurred in the 3 most severely damaged animals (Nos. 4, 10 and 24) were preceded by widespread EEG discharges. These latter began up to ½ s before the movements, implying a central origin for the discharges and a causal relationship to the jerks (Halliday, 1967). The discharges (fig. 10) were of earlier onset over the left hemisphere, which was also the site of localized subclinical seizure activity, and showed secondary bilateral synchrony. Myoclonus is reported following hypoxic-ischæmic episodes in man, both in survivors where it may be induced by movement, and in those dying in coma where it is spontaneous and rhythmic (Lance and Adams, 1963; Pampiglione and Harden, 1968; Madison and Niedermeyer, 1970). In contrast with those in the present animals the associated EEG discharges commonly exhibit fairly precise and probably primary bilateral synchrony as in the patients with other types of widespread neuronal disease and myoclonus reported by Watson and Denny Brown (1953, 1955). Cerebellar damage is often present and sometimes considered to be the basis of post-anoxic intention myoclonus (Lance and Adams, 1963). In the present study damage was confined to the cerebral hemispheres and principally the cortex, although it also involved the outer segment of the globus pallidus, the striatum or caudate nuclei.

In the baboon, in contrast to the rat, it was necessary to occlude both common carotid arteries during hypoxia in order to abolish the EEG and to produce brain damage which was of typical boundary zone distribution. As the intracranial pressure fell in each baboon after occlusion of the left artery and in 11 out of 17 after occlusion of the right (unchanged in 4), it is likely that sequential carotid occlusion led to some reduction in hemispheric perfusion compared with that during hypoxia alone. This is not surprising if the circle of Willis is functionally as well as anatomically similar to that of man in whom the vertebrobasilar system contributes only 15 per cent of total cerebral blood flow (Jennett *et al.*, 1976). The corresponding figure is 30 per cent for the macaque monkey (Dumke and Schmidt, 1943) but it is not known for the baboon. Thus, when both common carotid arteries are occluded it is most unlikely that normal hemispheric blood flow could be maintained from the vertebrobasilar system and collateral sources (detailed by Jennett *et al.*, 1976).

It is well known that there is a gradient of blood pressure from the origin of a major cerebral artery such as the MCA distally along its pial branches (Symon, 1967). At the junction of the three cortical arterial territories in the floor of the intraparietal sulcus the reduction in perfusion pressure will be greatest as this site is most remote from the origin of the three arteries at the circle of Willis (Zülch and Behrend, 1961). The reduced blood flow at this site and also to a lesser extent along the arterial boundary zones justifies the use of the term oligæmia in order to distinguish it from ischæmia, in which blood flow is arrested and with it the delivery of oxygen and substrate and the removal of waste products.

If arterial oxygen tension is normal, the degree and duration of hypotension required to produce critical local oligæmia along the boundary zones is such that spontaneous respiration fails early and mechanical ventilation has to be employed (Brierley and Excell, 1966; Brierley *et al.*, 1969). In the present study arterial oxygen tension in the range 20 to 24 mmHg cannot alone be responsible for the observed localization of damage as all regions were perfused with blood of the same oxygen tension. By using a PaO_2 just compatible with the retention of spontaneous respiration it has been possible to show that the oligæmia brought about by added bilateral common carotid artery occlusion can reduce tissue oxygenation to the level critical for EEG failure as early as 23 s or as late as 44 min. The ability to manipulate the EEG locally at the depth electrodes in the confluence of the arterial boundary zones by small alterations in PaO_2 which had no effect on systemic circulation, was a reminder of how close to 'threshold' the supply of oxygen was. This 'threshold' could be crossed reversibly by a simple reduction in blood oxygen content due to a small decrease in PIO_2. Not only the local EEG failure but also the localized damage along the boundary zones must be ascribed to a critical local reduction in oxygen supply. The same situation can be brought about if the PaO_2 is unchanged but there is some reduction in cerebral perfusion pressure as in the 8 animals with a slow secondary fall in mean arterial BP.

From Table 3 it can be seen that minor brain damage (scores 1–8) results from 14 to 25 min of bilateral carotid occlusion during hypoxia (but only 9 to 16 min of EEG silence during occlusion). In *Macaca Mulatta* cerebral circulatory arrest must be at least 15 min for brain damage to occur (Nemoto, Bleyaert, Stezoski, Moosy, Rao and Safar, 1977). If the period of arrest was 16 min there was widespread cortical damage up to the level of infarction. In the baboons of the present study, the longest period of bilateral carotid occlusion was 63 min (with 28 min of near-silent EEG) yet in the brain of this animal the central portions of the cortical arterial territories were entirely normal.

In the dog Steen, Michenfelder and Milde (1979) compared the effects of 10 to 12 min of incomplete cerebral ischæmia with 8 to 9 min of complete ischæmia (Steen, Milde and Michenfelder, 1979). Complete ischæmia was produced by simultaneous occlusion of the ascending aorta, inferior and superior (above the azygos vein) venæ cavæ. Incomplete ischæmia was obtained by removal of blood through wide femoral cannulæ. Complete ischæmia of 8 to 9 min resulted in severe neurological impairment, while if cerebral blood flow was reduced to less than 10 per cent of normal, a period of incomplete ischæmia of 12 min was needed to produce a comparable neurological deficit.

Jackson and Dole (1979), also in the dog, produced total cerebral ischæmia by inflating balloons in the aortic arch and inferior vena cava. After 12 min total cerebral ischæmia some low voltage, slow EEG waves returned between 90 min and 48 h after deflation of the balloons. In no animal did the EEG ever return to normal and 6 of 15 animals died in a decerebrate state within 24 h and not because of cardiopulmonary complications.

Thus, these studies in the baboon (present series), monkey and dog provide no support for the contention of Siesjö (1978) and Rehncrona, Mela and Siesjö (1979) that a considerable reduction in cerebral blood flow is a more serious insult than cerebral circulatory arrest. However, it is important to stress that the latter had been achieved in the rat, not by arrest of the heart or any occlusion of arteries supplying the brain, but by raising the pressure of the cerebrospinal fluid above that of systolic blood pressure, a method devised by Neely and Youmans (1963). Total cerebral ischæmia lasted 30 min (Nordström, Rehncrona and Siesjö, 1978*a*). This model of 'bloodless' or 'compression' ischæmia is entirely different from cardiopulmonary arrest in man and from the models in primate and dog already discussed. Further, the capacity of this model for survival, with or without neurological deficit, is unknown, but typical ischæmic cell change was observed in the brains of rats that had been submitted to only 10 to 15 min of 'compression' ischæmia (Brierley, Ljunggren and Siesjö, 1975). Incomplete ischæmia (also 30 min) in the rat was induced by bilateral common carotid clamping while the mean arterial BP was reduced to 50 mmHg (Nordstrom *et al.*, 1978*b*). Neurophysiological, neurological and neuropathological sequelæ have not been described after survivals of more than 90 min and the greater detrimental effect of incomplete compared with complete ischæmia rests solely on metabolic data in the two very different experimental models.

This study in the baboon has demonstrated that the well-known arterial boundary zone distribution of ischæmic neuronal destruction can be the result of a combination of hypoxia and the oligæmia produced by transient bilateral common carotid artery occlusion. Most probably, a similar combination is responsible for the majority of instances of boundary zone damage in the human brain (including the hind-brain).

Although the systemic and cerebral vessels of the baboons were always free of disease, anatomical anomalies were present in 3 of the 20 animals. These included one with asymmetry of the common and internal carotid arteries of one side compared to the other, with absence of the ACA on the smaller side, one with absent and one with thread-like posterior communicating arteries. The incidence of anatomical anomalies may be higher in man. Alpers and Berry (1963) examined 350 normal brains and found that the circle of Willis was anatomically normal in only 52 per cent. This proportion fell to 37 per cent in the presence of aneurysms and to 33 per cent in the presence of infarcts. String-like posterior communicating arteries occurred in 22 per cent of normal brains and in 40 per cent of those with aneurysms. While these anatomical variations are of no significance in the healthy subject they may contribute to a critical reduction in oxygen supply if there are additional factors such as systemic hypotension, hypoxia or occlusive disease of extra- and/or intracerebral arteries. They may also increase the risk of deliberate temporary or permanent occlusion of a common or internal carotid artery and also the use of elective hypotensive anæsthesia.

Occlusive vascular disease, particularly on the basis of atheroma, plays an exceptional role in determining the site and extent of boundary zone lesions. Thus, if carotid stenosis is grossly asymmetrical the boundary zone lesion may be entirely unilateral. A hypotensive episode in a subject with severe bilateral carotid stenosis may give rise to bilateral boundary zone infarcts in the absence of embolism or of intracerebral vascular disease (Adams, 1967). As the phenomenon of autoregulation of cerebral blood flow is dependent on the normality of the muscle and elastic elements of the arterial wall, increasing arteriosclerosis will progressively impair the capacity to maintain blood flow if arterial oxygen tension should fall or there is reduced perfusion pressure at a systemic or local level.

The anatomical and pathological factors considered above may imply that the brain is at risk during certain surgical procedures. During coronary artery surgery, in particular, a by-pass may be used at a pressure which is adequate for all except cerebral perfusion. Russell and Bharucha (1978) described four patients undergoing coronary artery surgery with by-pass and hypothermia. All made a slow incomplete recovery from cortical blindness, visual disorientation and reading difficulties. Bilateral parieto-occipital damage was demonstrated and attributed to the combination of occlusive disease, particularly in the vertebrobasilar system, and perfusion pressures in the range 70 to 100 mmHg (pressures which had not been followed by neurological deficit in other patients). The authors stressed the importance of monitoring blood pressure, cerebral blood flow and the EEG.

The present study has shown a close relationship between the total scores for the continuously monitored EEG and the severity of brain damage, even when this was minor. In the clinical setting simple and inexpensive techniques for EEG monitoring are required. The present experiments have shown that a critical reduction in cortical oxygen supply is indicated by increasing periods of EEG suppression (scores 2–5) and impending brain damage by sustained electrical silence. Expensive frequency analysis techniques are not necessary to demonstrate these EEG signs. Similar information to that given by the total visual or computerized EEG scores has been obtained from an unsophisticated monitoring device using two scalp electrodes in the parietal regions, the cerebral function monitor (Maynard, Prior and Scott, 1969; Prior, 1979). The corresponding levels of activity relating to the present six-point scoring system are graphically presented with particular emphasis on periods of suppression or isoelectric EEG (Prior *et al.*, 1978) and the device has been found a practical and accurate means of predicting post-operative neurological deficit in patients undergoing open cardiac surgery (Schwartz, Colvin, Prior, Strunin, Simpson, Weaver and Scott, 1973).

This study has shown that irreversible neuronal damage along the arterial boundary zones occurs only after an appreciable period of EEG silence. This period can be as short as 8 min (No. 3) during bilateral common carotid occlusion. Conversely, a period of electrical silence of up to 9½ min duration during bilateral carotid occlusion was not followed by brain damage (animals Nos. 14, 15 and 25). These findings endorse the concept of two ischæmic thresholds (Astrup, Symon, Branston and Lassen, 1977). The earlier is that of failure of electrical activity and the later is that of the inception of irreversible neuronal damage. It is also evident that during anæsthetic and surgical procedures when the brain is at risk EEG monitoring, even in its most simplified form, can clearly identify the earlier threshold so that appropriate remedial action can be taken without delay.

The present experimental study has demonstrated that reduced cerebral perfusion in conjunction with hypoxia has the capacity to produce typical ischæmic damage along the arterial boundary zones. This has particular relevance to the intensive care of the unconscious patient with head and other injuries in whom additional ischæmic brain damage may be avoidable (Reilly, Adams, Graham and Jennett, 1975; Miller, Sweet, Narayan and Becker, 1978). In procedures such as cardiac surgery, carotid surgery, dental anæsthesia in the seated posture and in hypotensive anæsthesia, the same combination, but particularly with the addition of often unsuspected occlusive vascular disease or congenital anomaly, may add the hazard of brain damage.

SUMMARY

The pathogenesis of ischæmic neuronal damage along the arterial boundary zones of the forebrain was investigated in 20 lightly anæsthetized, spontaneously breathing baboons. A combination of bilateral common carotid artery occlusion and systemic hypoxia was used. An arterial PO_2 of 21.2 ± 2.5 mmHg was maintained for about 20 min. Additional occlusion of the left common carotid artery for 20 min had no effect on the EEG (except for one animal with a cerebrovascular anomaly). Only when occlusion of the right carotid artery was added did the EEG become almost or completely isoelectric after an interval ranging from 23 s to 44 min (sequential common carotid artery occlusion while breathing air did not affect the EEG). After a chosen period of electrical silence, hypoxia and carotid occlusion were terminated. Hypotension did not occur during carotid occlusion or the recovery period. Survival was deliberately limited to 46 h, during which neurological assessment was made and the EEG was recorded just before *in vivo* perfusion-fixation of the brain. Neurological deficits included asymmetrical quadriparesis and myoclonus epilepsy. The brains of 3 animals were normal and in the 15 with brain damage this was restricted in the cerebral cortex to the arterial boundary zones. In the presence of profound hypoxia the oligæmia due to bilateral carotid occlusion can reduce tissue oxygenation locally to a level critical for the production of ischæmic damage in the cortical boundary zones. Portions of the basal ganglia were also involved in 7. The quantified brain damage scores correlated with the EEG scored on a six-point scale during the period of electrical silence and early recovery. Brain damage scores also correlated with the times for intracranial pressure to return to normal levels from the peaks recorded just after the end of arterial occlusion and hypoxia. As brain damage only occurred when the EEG during bilateral carotid occlusion and hypoxia was silent for at least 8 min, it was concluded that in a variety of clinical settings a simple EEG-based monitoring system would be optimal for the detection of an impending failure of cerebral oxygen supply.

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AN AUTORADIOGRAPHIC STUDY OF HUMAN GLIOMAS: GROWTH KINETICS OF ANAPLASTIC ASTROCYTOMA AND GLIOBLASTOMA MULTIFORME

by T. HOSHINO, J. J. TOWNSEND, I. MURAOKA *and* C. B. WILSON

(*From the Brain Tumor Research Center, Department of Neurological Surgery, and the Department of Pathology, University of California School of Medicine, San Francisco, California 94143, USA*)

INTRODUCTION

THE classification of gliomas continues to be a subject of debate—partly because their pathology has been developed on the basis of recognizable cytomorphological and histopathological patterns, with only vague consideration of their developmental evolution (oncogenesis) and biological behaviour. It was Bailey and Cushing (1926) who first attempted to identify the cell types in gliomas by comparing them with the cells of normal tissue at various developmental stages. By this method, Bailey and Cushing were able to arrange the large group of tumours labelled glioma by Virchow in an orderly system of classification. Though criticized and modified by many pathologists, the system of Bailey and Cushing remains, with only minor changes, the basis for diagnosis and treatment of intracranial tumours.

As a result of the increasing attention that has been directed to the important part played in the development of certain gliomas by anaplasia (or anaplastic changes including vascular alterations), a system of histological grading was introduced by Kernohan and Sayre (1952). This system has not been widely adopted by neuropathologists and has sometimes been vigorously attacked. Despite considerable individual variation, however, there is a positive correlation between the histological grade and the interval from the primary operation until recurrence.

Much confusion persists, and we suspect that it stems from the present lack of fundamental knowledge about the growth kinetics and/or biological behaviour of the various tumour types. We do not know what the mechanism of de-differentiation is or how anaplastic changes should be interpreted or whether such alterations are primary, secondary, or independent phenomena. Furthermore, the difficulty in understanding the evolution of a given tumour is increased by our inability to observe it dynamically from moment to moment.

During the past ten years, the authors have had the opportunity to study some aspects of the biological activity in the astrocytoma-glioblastoma series as part of a larger study of cell kinetics in human gliomas (Hoshino, Barker, Wilson, Boldrey and Fewer, 1972; Hoshino, Wilson, Rosenblum and Barker, 1975; Hoshino, Barker and Wilson, 1975; Hoshino, Wilson and Ellis, 1975; Hoshino and Wilson, 1979). In the present study, we performed autoradiographic analyses of the biopsy and autopsy specimens from patients injected either intra-arterially or intravenously with tritiated thymidine. By studying the proliferative behaviour of each neoplastic cell, as well as certain normal cells contained within the tumours, we endeavoured to determine whether the proliferative behaviour of the individual cells comprising a tumour was useful in characterizing well differentiated astrocytoma, anaplastic astrocytoma and classic glioblastoma multiforme.

PATIENTS AND METHODS

Nine patients with gliomas verified by autopsy findings (5 glioblastoma multiforme, 3 anaplastic astrocytoma, one mixed glioma) were studied. Table 1 presents clinical data on the study subjects: the patient's age at death, treatments before and after labelling with ^{3}H-Thymidine (^{3}H-TdR) with a specific activity of 0.36 Ci/mmol (New England Nuclear, Boston, Mass.), length of illness, cause of death, and pathological diagnosis at autopsy.

With informed consent of the patients and authorization from appropriate officials of our institution (The University of California, Committee on Radioisotopes, Radiation Safety and Human Experimentation), ^{3}H-TdR was administered shortly before craniotomy to the 9 patients—5 mCi intra-arterial ^{3}H-TdR to 6 of the patients, and 10 mCi intravenous ^{3}H-TdR to the other 3.

TABLE 1. CASE HISTORIES OF STUDY SUBJECTS

Patient	*Age (yrs) /sex*	*Treatment pre-^{3}H-TdR*	*Treatment post-^{3}H-TdR*	*Survival (total)*	*Cause of death*	*Pathology at autopsy*
1	42/M	Craniotomy 10/71 Chemotherapy (BCNU*)	Craniotomy 2/72	10 mo	Pulmonary embolism	L. parieto-occipital glioblastoma
2	53/M	Craniotomy 11/72 Chemotherapy (CCNU**)	Craniotomy 3/73	7 mo	Herniation	R. temporo-parietal glioblastoma
3	17/M	Craniotomy 3/68 Radiotherapy (5515 rad)	Craniotomy 1/69 Chemotherapy (BCNU)	18 mo	Herniation	L. frontal glioblastoma
4	42/M	Craniotomy 6/69, 12/71 Radiotherapy (5000 rad) Chemotherapy (CCNU)	Craniotomy 2/73 Chemotherapy (CCNU, vincristine, procarbazine)	4 yr	Herniation	L. fronto-parieto-temporo-occipital glioblastoma
5	59/M	Craniotomy 9/75 Radiotherapy (5400 rad + hydroxyurea)	None	20 mo	Herniation	R. parietal glioblastoma
6	52/M	Craniotomy 1/72	Craniotomy 4/72 Radiotherapy (5000 rad) Chemotherapy (BCNU)	7 mo	Pulmonary embolism	R. temporal anaplastic astrocytoma
7	55/M	None	Craniotomy 6/70	4 mo	Pulmonary embolism	R frontal anaplastic astrocytoma
8	31/M	Craniotomy 7/67 Radiotherapy (5000 rad) Chemotherapy (BCNU)	Craniotomy 1/70 Chemotherapy (BCNU)	7 yr	Herniation	L. frontal anaplastic astrocytoma
9	47/M	Craniotomy 11/62 Radiotherapy (5000 rad)	Craniotomy 6/69 Chemotherapy (BCNU)	14 yr	Herniation (hæmorrhage into tumour)	L temporal mixed glioma

* BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea. ** CCNU = 1,(2-chloroethyl)-3-cyclohexyl-1-nitrosourea.

Tissue excised at operation was fixed in 10 per cent buffered formalin and embedded in paraffin. The tumours were classified histologically using hæmatoxylin-eosin, phosphotungstic acid-hæmatoxylin (PTAH), hæmatoxylin van Gieson, and Laidlaw's reticulin stains. All 9 patients died, most from recurrence of the tumour, after post-operative intervals ranging from three weeks to seven years, and autopsies were performed. Brain tissue and tumour obtained at autopsy were prepared by the same methods as biopsy specimens. To obtain autoradiographs of each biopsy and autopsy specimen, sections 4 μm in thickness were made from the paraffin blocks and mounted on glass slides, deparaffinized, dipped in a nuclear emulsion (Kodak NTB 3), and exposed in light-tight boxes at 4° C for four to eleven months. The slides were then developed with Kodak D-19 or Microdol for four minutes, fixed with acid, and stained with either 0.25 per cent toluidine blue, hæmatoxylin, or hæmatoxylin-eosin.

A labelling index (LI) was obtained for each specimen by determining the percentage of thymidine-labelled cells in the total cell population. With the background averaging less than one grain per nucleus, cells were scored as labelled if each of their nuclei contained more than four grains. Labelling depends upon penetration of radioactive material into the area to be examined; and ^{3}H-TdR penetration is impeded in areas where blood flow is impaired, as indicated by tissue necrosis and other visible degenerative changes. Therefore, the presence of even a few labelled cells in an area was accepted as indicating that all cells had been exposed to ^{3}H-TdR, and differential labelling studies within a given area were deemed to yield a valid average LI. Routinely, 10 to 20 viable areas of each biopsy specimen were selected from the tumour centre, and 1000 to 3000 neoplastic cells from each area were examined. From the autopsy specimens, however, only heavily labelled areas (the most retarded areas in terms of proliferation) were used to determine the LI. Since most actively dividing malignant gliomas dilute tagged DNA very quickly, scoring of areas of active proliferation reduces the LI unnecessarily.

For this study, glioblastoma multiforme was defined as a glial neoplasm with the histological characteristics of marked hypercellularity, extreme nuclear pleomorphism, numerous mitoses, pseudopalisading around areas of tumour necrosis, and marked endothelial hyperplasia of capillaries. Anaplastic astrocytoma was defined as a tumour consisting predominantly of astrocytes with moderate nuclear pleomorphism, a variable degree of endothelial hyperplasia of capillaries, and mitoses in at least some portions of tumour. Anaplastic changes were described in detail in order to characterize individual differences between tumours.

RESULTS

Histological Findings

Patients 1 and 2. The tumours of Patients 1 and 2 demonstrated at biopsy and autopsy all the characteristics of glioblastoma multiforme. Patient 2 had extensive seeding throughout the ventricular system and also, to a limited degree, in the meninges, especially over the right cerebellar hemisphere adjacent to a cerebellar tumour.

Patient 3. The glioblastoma multiforme of Patient 3 was unusual for its occurrence in a 15-year-old boy. Both biopsy findings and autopsy eighteen months later showed leptomeningeal seeding and a large population of bizarre giant cells. The majority of tumour cells were primitive glial cells or giant cells measuring up to 150 μm in diameter and having a very irregular contour. Some contained one or more multilobular nuclei with eosinophilic inclusions or nuclear vacuoles, others contained multiple small, pale nuclei, either tightly packed or forming a crescent on the cell periphery.

Patient 4. At autopsy, the tumour of Patient 4 contained numerous multinucleated giant cells similar to those of Patient 3. The tumour was originally diagnosed as a gemistocytic astrocytoma, and the patient received radiation and chemotherapy. A third biopsy in 1973 revealed all the characteristics of glioblastoma multiforme except that the specimen did not contain the multinucleated giant cells found at autopsy. Considering this patient's unusually long survival (four years), it is most likely that the tumour originated as an anaplastic astrocytoma and then progressed to a glioblastoma.

Patient 5. Similarly, the biopsy specimen from Patient 5 was diagnosed as anaplastic astrocytoma, but autopsy demonstrated a glioblastoma multiforme with focal accumulation of neoplastic fibrillary astrocytes.

Patient 6. The tumour of Patient 6 was diagnosed as glioblastoma multiforme (tissue not available for review) at the initial craniotomy in January 1972. The tissue obtained in April 1972 revealed aggressive features such as necrosis, endothelial proliferation, pleomorphism, mitoses and giant cells, but lacked typical pseudopalisading around necrotic areas. Autopsy demonstrated a diffuse glioma with pleomorphic cells (mainly astrocytes with giant cells), proliferating blood vessels, large necrotic areas at its centre, and small, better-differentiated fibrillary astrocytes on the periphery. These findings were diagnostic of an anaplastic astrocytoma diffusely infiltrating the surrounding tissue.

Patient 7. The tumour of Patient 7 was histologically very cellular, the majority of the cells being astrocytes that ranged from gemistocytic to stellate and elongated pilocytic forms. They stained uniformly with the PTAH method, varying only in density of glial fibres. There was no tendency to giant cell formation, but scattered mitotic figures were present. In some areas, the tumour was avascular, with a microcystic pattern that diffusely infiltrated grey and white matter. In other areas, the tumour demonstrated endothelial proliferation and necrosis with pseudopalisading. An unusual feature was the multicentric nature of the tumour, which had multiple foci in the cerebral hemispheres.

Patient 8. The tumour of Patient 8 began as a typical anaplastic astrocytoma, composed mainly of fibrillary astrocytes. Between the first and second biopsies, large numbers of giant astrocytes appeared within the tumour, due perhaps to irradiation and/or chemotherapy. Typical giant cells were elongated (measuring 60 to 70 μm in their greatest diameter) and the nuclei contained prominent nucleoli. Mitoses were rare. The cytoplasm formed multiple tapering processes filled with coarse glial fibrils. The second biopsy showed an increase in the number of gemistocytes and a decrease in the number of stellate and bipolar fibrillary astrocytes. At autopsy, histology revealed a cellularly compact, largely avascular, and minimally necrotic lesion with a nearly uniform cell structure. The cells were virtually all astrocytes. The majority of these were monstrous, with multiple branching processes; but there were occasional foci of gemistocytes or small cells resembling oligodendrocytes. The cells were pleomorphic and occasionally multinucleated. Mitoses were rare. Small scattered foci of necrosis associated with sudanophilic fat were accompanied by vascular proliferation (some vessels thick-walled, others thin-walled and telangiectatic, with or without thrombi). PTAH and Holzer stains demonstrated abundant production of glial fibres.

Patient 9. The tumour in the left frontal lobe of Patient 9 was considered a fibrillary astrocytoma at biopsy in November 1962. Biopsy seven years later showed the same histological characteristics. The ^{3}H-TdR was administered before the second craniotomy, and the patient lived another seven years. Examination of the brain at autopsy revealed an acute hæmorrhage into an area of residual tumour composed of astrocytes and oligodendroglia. The tumour extended throughout the left fronto-temporo-parietal areas. There were multiple clear, cystic spaces and also areas of increased vascularity consisting of thin-walled vessels without endothelial proliferation. There was also focal perivascular cuffing by lymphocytes. Reactive astrocytes with abundant cytoplasm were found on the periphery. The oligodendroglial elements are characterized by small, round nuclei surrounded by a clear halo. The astrocytes showed only moderate pleomorphism; the majority contained small nuclei with recognizable cytoplasm.

Labelling Index Study

The LIs for biopsy and autopsy specimens are given in Table 2. The LI of biopsy material represents an average of all viable areas counted, since labelling varied from area to area within each specimen. The ranges of LIs were obtained from groups of approximately 1000 cells each from various areas within individual tumours. The LI varied from one glioma to another and from one area to another within a tumour; but, as we have previously reported (Hoshino *et al.*, 1972, Hoshino, Wilson and Ellis, 1975; Hoshino and Wilson, 1979), the LI of a particular

TABLE 2. LABELLING INDICES [LIs] OF BIOPSY AND AUTOPSY SPECIMENS

Patient	*^{3}H-TdR (mCi)**	*Biopsy*		*Survival post-^{3}H-TdR*	*Autopsy LI±SD (%)***
		LI±SD (%)	*Range (%)*		
1	5 i.a.	8.6±3.1	5.4–16.6	4 mo	0.1***
2	5 i.a.	15.9±3.4	12.2–21.0	2 mo	0.1***
3	5 i.a.	11.3±3.9	7.1–17.8	5 mo	2.0±0.5
4	5 i.a.	11.0±1.4	8.9–12.8	2 mo	7.1±0.8
5	5 i.a.	—	—	1 mo	7.5±3.5
6	5 i.a.	5.1±1.2	3.4–6.3	2 mo	4.8±1.4
7	10 i.v.	2.2±0.8	0.4–3.0	3 wk	1.6±0.4
8	10 i.v.	8.3±2.7	4.6–11.3	6 mo	0.1***
9	10 i.v.	0.9±0.1	0.8–1.1	7 yr	0.1***

* i.a. = intracarotid injection; i.v. = intravenous injection. ** Most heavily labelled area.
*** Too few to measure.

area correlated reasonably well with the histology of that area. In this study, LIs for the glioblastomas averaged 11.7 per cent, and for the anaplastic astrocytomas, 5.2 per cent. All the patients except No. 9 (whose tumour was a mixed glioma) died within six months of the operation at which ^{3}H-TdR was administered.

The LIs are lower in autopsy specimens because each daughter cell receives one-half of the labelled DNA upon cell division; and after several successive mitoses, the cells do not carry enough ^{3}H-bound DNA to be identifiable by conventional autoradiographic techniques. This dilution was detected after as little as two to three weeks when 10 mCi of ^{3}H-TdR was administered intravenously, and after one to two months when 5 mCi of ^{3}H-TdR was administered intra-arterially. The highly anaplastic areas containing numerous mitoses and undifferentiated pleomorphic cells in Patients 5 and 7 had LIs of less than 0.1 per cent. Inclusion of such areas in the LI study would have the effect of deceptively lowering the average LI until it would be so far from the mean of the tumour that it would have no bearing on the biological behaviour of the tumour. To circumvent this artefact, the average LI in material from autopsy was obtained from the most heavily labelled areas, which were assumed to represent the areas of tumour that were least active and therefore least affected by dilution of ^{3}H-bound DNA as a result of frequent mitoses.

Two glioblastomas (Patients 1 and 2) showed very little labelling throughout. By contrast, the glioblastomas of Patients 3, 4 and 5 demonstrated foci of heavily labelled cells (yielding LIs of, respectively, 2.0 per cent, 7.1 per cent, 7.5 per cent) up to five months after administration of ^{3}H-TdR. At autopsy, the anaplastic astrocytomas of Patients 6 and 7 revealed foci of heavy labelling similar to those of Patients 3, 4 and 5. However, Patient 8, who harboured an anaplastic astrocytoma to which 10 mCi of intravenous ^{3}H-TdR was administered six months prior to the patient's death, demonstrated almost no labelling within the tissue examined. Longer survival was associated with the presence of foci of heavy labelling—in contrast with other tumours in which dilution of ^{3}H-bound DNA was uniform throughout. Patients 6 and 7 died of pulmonary emboli unrelated to tumour growth and were, thus, exceptions to this. Patient 9, who harboured a mixed glioma, retained a few labelled cells when he died seven years after the intravenous administration of 10 mCi of ^{3}H-TdR.

Autoradiographic Findings

Surgical specimens. The types of cells labelled and the distribution patterns of labelled cells were similar to previously reported observations (Hoshino *et al.*, 1973; Hoshino, Wilson and Ellis, 1975). The labelled cells included fibrillary, protoplasmic, poorly differentiated astrocytic, oligodendroglial and ependymal cells. Endothelial cells and adventitial fibroblasts, as well as desmoplastic fibroblasts, were frequently labelled, whereas gemistocytic astrocytes, macrophages, and polymorphonuclear leucocytes failed to incorporate ^{3}H-TdR. Lymphocytes, whether scattered within a glioma or surrounding the vessels, were rarely labelled, though in Patient 8 perivascular lymphocytes and/or plasma cells showed labelling

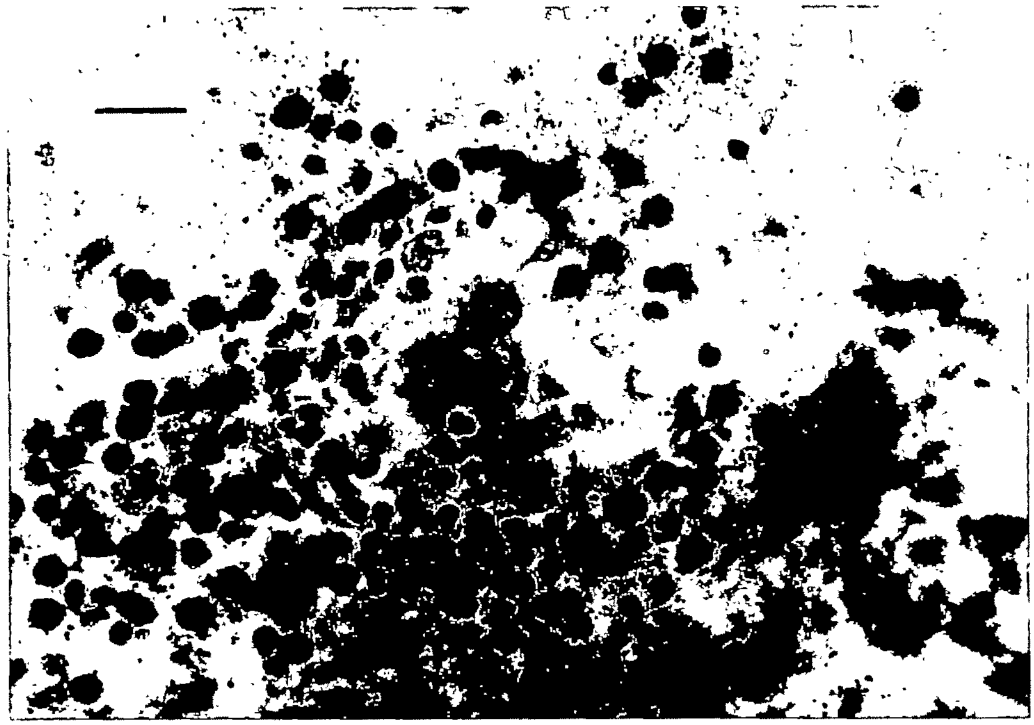

FIG. 1. Labelled perivascular lymphocytes and/or plasma cells of anaplastic astrocytoma (*Patient 8*). Toludine blue. Bar = 20 μm.

comparable to the surrounding neoplastic cells (fig. 1). Single, multinucleated giant cells with abundant cytoplasm were rarely labelled. Astrocytes palisading around areas of necrosis did not show labelling, while similar neoplastic astrocytes adjacent to them frequently did.

Autopsy specimens. Autoradiograms prepared from Patients 1 and 2 showed sparse, scattered labelling of cells (3 to 4 per slide). The labelled cells included capillary endothelial cells, gemistocytes, and macrophages. Almost all of the neoplastic glial cells seemed to dilute their ^{3}H-bound DNA in two to four months. An unusual finding was the presence in Patient 1 of labelled cells in œdematous tissue that was devoid of neoplastic cells; these labelled cells included: cells similar to oligodendroglia, with halos and round nuclei; cells like astrocytes, with oval nuclei and fibrillary processes; cells like microglia, with slender, irregular nuclei; and endothelial cells of capillaries.

The other three glioblastoma patients (Nos. 3, 4 and 5) exhibited a variety of labelled cells. In general, the malignant areas exhibiting dense cellularity, abnormal vessels, pleomorphism and mitoses lacked labelled tumour cells. Tissue obtained from Patient 3 five months after an intracarotid injection of ^{3}H-TdR demonstrated

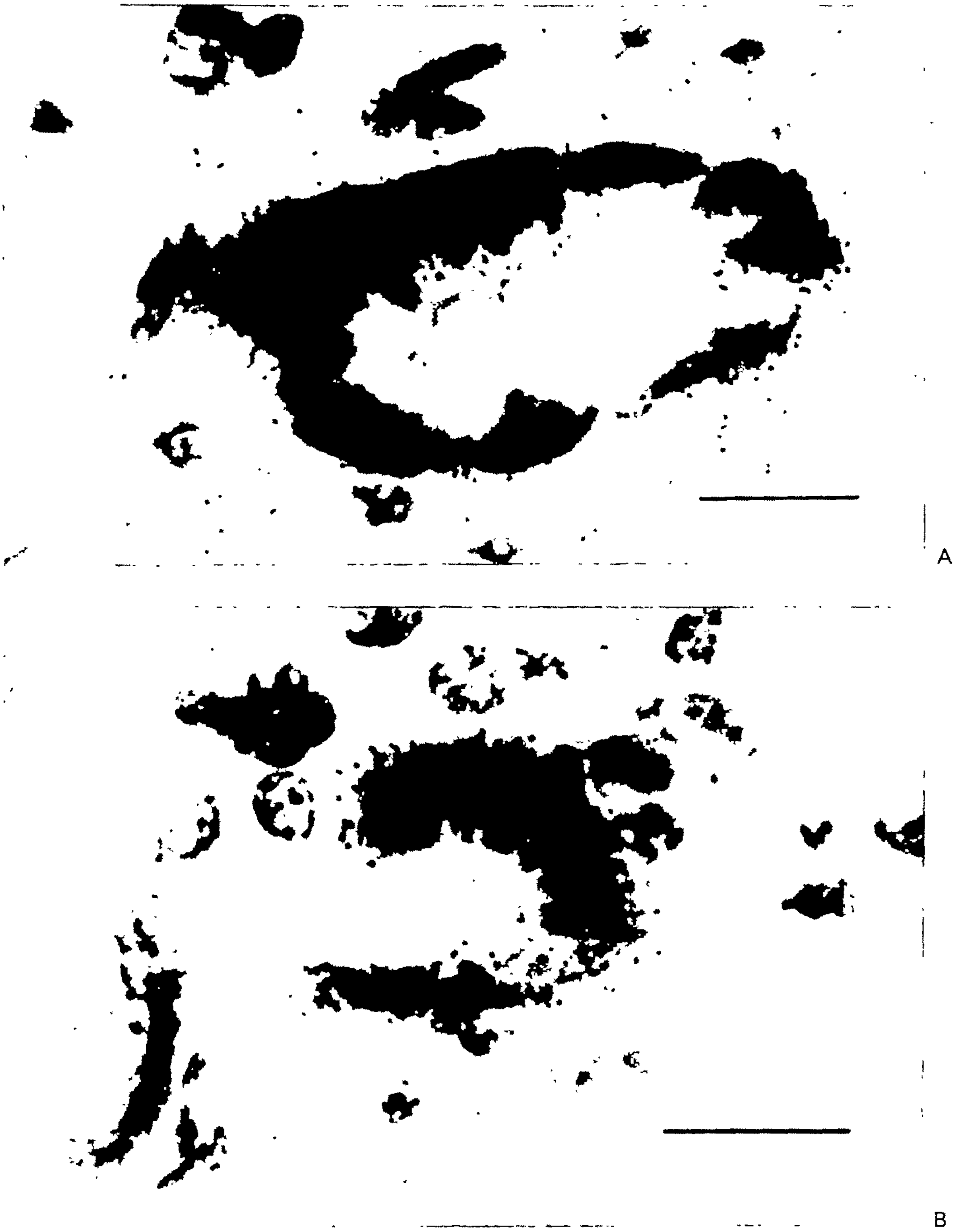

FIG. 2. A and B. Labelled multinucleated giant cells of glioblastoma (*Patient 3*). Hæmatoxylin. Bar = 50 μm.

a few labelled cells in anaplastic areas, while the majority of the poorly differentiated tumour areas contained no labelled cells. Foci of gemistocytic astrocytes together with well differentiated astrocytes showed a considerable number of labelled cells. The specimens from Patient 4 also showed foci of more heavily labelled cells, although the majority of the poorly differentiated areas contained very few, if any, labelled cells. The labelled cells included neoplastic astrocytes, endothelial cells, microglia and multinucleated giant cells. The nuclei in most of the multinucleated giant cells (which were not found in the biopsy tissue) showed very heavy labelling (fig. 2). Marginal zones and normal brain tissue adjacent to the tumour also exhibited a few labelled cells: astrocytes (probably reactive), endothelial cells, and microglia. Perivascular lymphocytes and foamy macrophages in large necrotic areas were not labelled.

In the tumour of Patient 5, the anaplastic areas contained only scattered labelled cells, some of which had only a few grains per nucleus. Areas with many gemistocytic astrocytes and occasional necrotic foci showed a considerable number of labelled cells, including gemistocytes, neoplastic astrocytes, and endothelial cells. Moderately numerous grains were present on gemistocytes. Well differentiated areas adjacent to gemistocytic and/or anaplastic areas showed fewer labelled cells than these areas, but the number of grains per nucleus was greater than in the gemistocytic areas (fig. 3). One pleomorphic cellular area with numerous mitoses

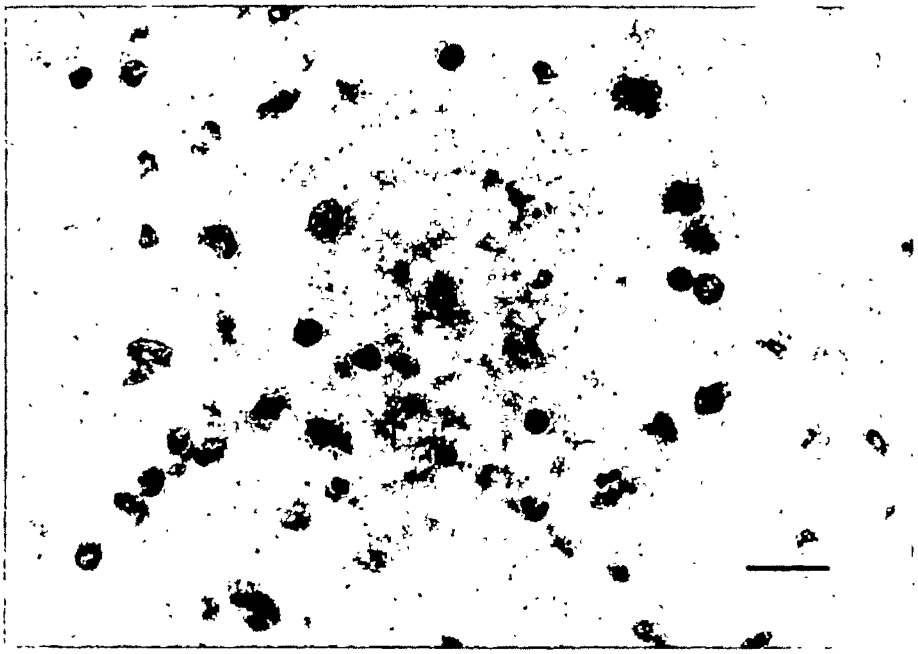

FIG. 3. Heavily labelled cells of well differentiated areas of glioblastoma (*Patient 5*). Hæmatoxylin. Bar = 50 μm.

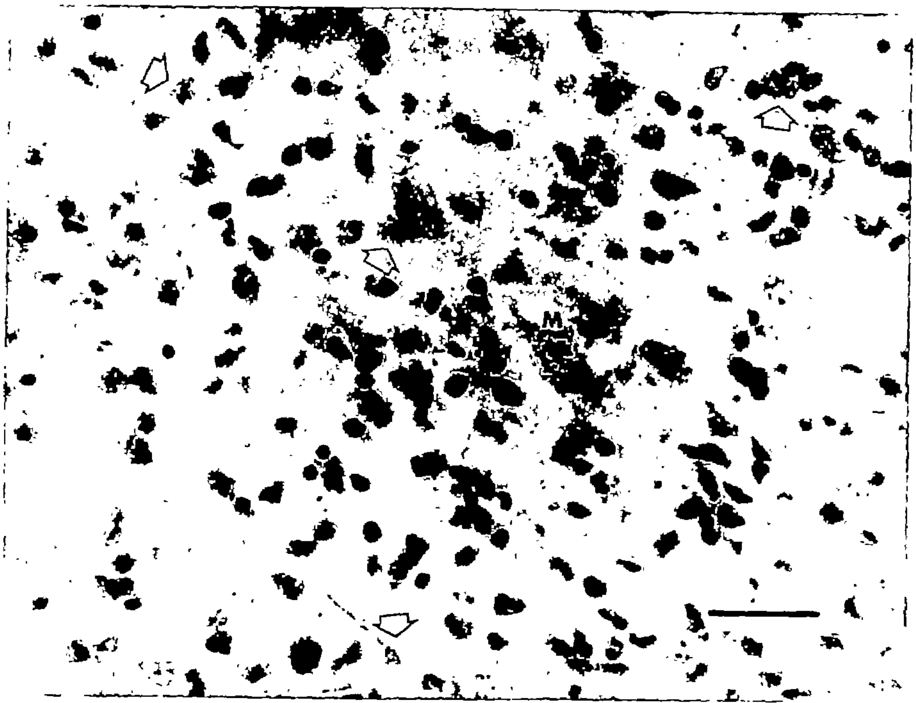

FIG. 4. Pleomorphic cellular area from the same tumour shown in fig. 3 (*Patient 5*), showing mitosis (M) and labelled cells with fewer grains (arrow). Hæmatoxylin. Bar = 100 μm.

and giant cells but no necrosis contained fewer labelled cells (fig. 4) than the well differentiated area or the less cellular paraventricular area. The paraventricular area, which was partly invaded by tumour cells, contained heavily labelled cells (fig. 5) that appeared neoplastic, though some may have been reactive subependymal astrocytes. Lymphocytes that cuffed vessels both within the tumour and outside it were not labelled.

The specimens of anaplastic astrocytoma from Patient 6 likewise showed poor labelling of most of the pleomorphic areas, but several foci of pleomorphic cells showed labelling. One pleomorphic area near the subarachnoid space demonstrated labelled endothelial and fibroblastic cells. Some labelled cells were found in areas with a streaming pattern of neoplastic glial cells (which were bipolar but moderately pleomorphic). Macrophages in areas of focal necrosis were also labelled. Small numbers of tumour cells were found around the third ventricle, but the few labelled cells in this area appeared to be reactive subependymal astrocytes (fig. 6). Occasionally, the heavily labelled cells in normal-looking brain at the tumour margin had dense chromatin and round nuclei, and appeared to be oligodendroglia. Astrocytic cells (probably neoplastic) were also labelled with a varying number of grains.

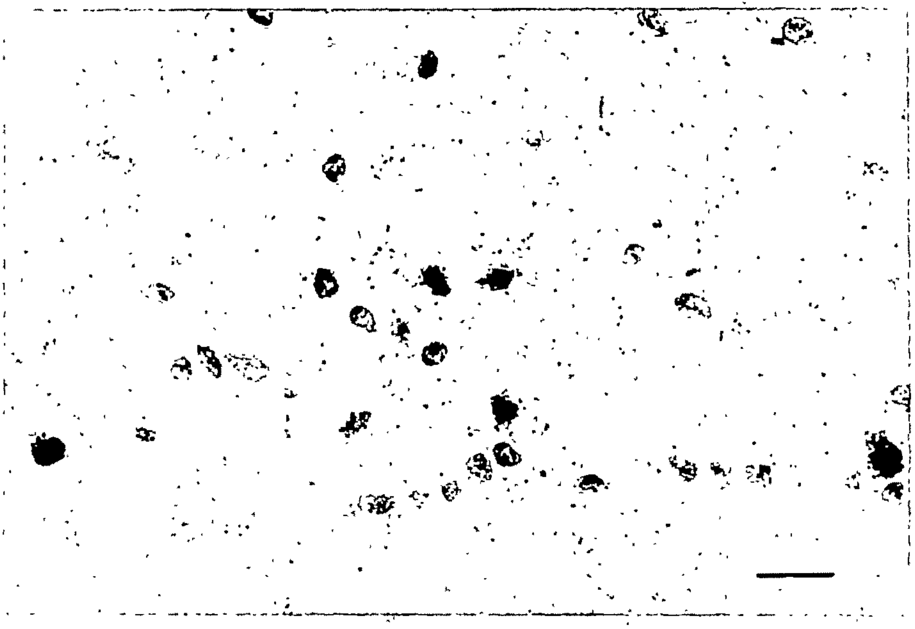

FIG. 5. Paraventricular area from the same tumour shown in figs. 3 and 4 (*Patient 5*), showing several heavily labelled areas. Hæmatoxylin. Bar = 50 μm.

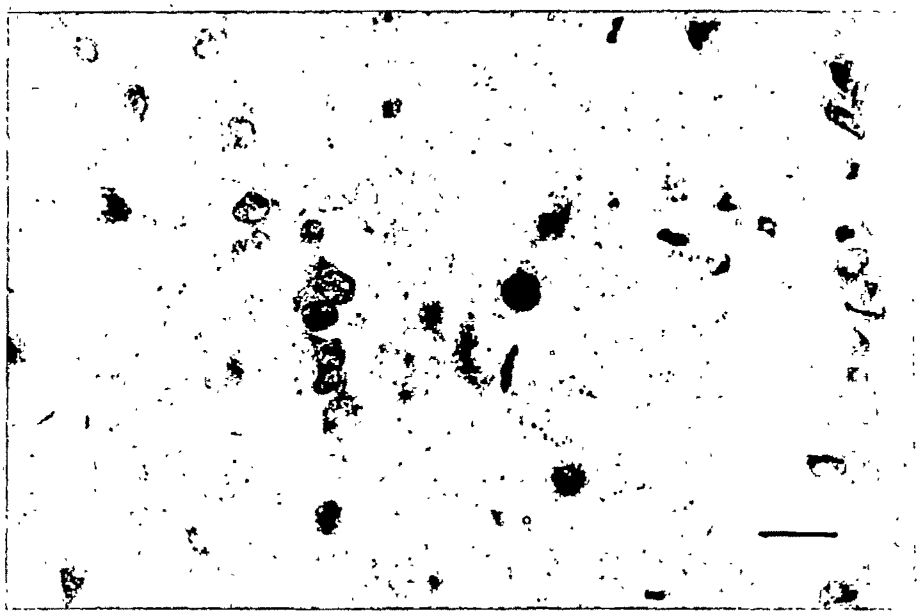

FIG. 6. Labelled subependymal cells (*Patient 6*). Hæmatoxylin. Bar = 50 μm.

Tissue obtained from Patient 7, another anaplastic astrocytoma, was labelled similarly to that of Patient 6. Pleomorphic, cellular areas with anaplastic features and mitoses showed fewer labelled cells. Well differentiated astrocytes in less cellular areas contained a higher frequency of heavily labelled cells. Some elongated nuclei (suggestive of fibroblasts), endothelial cells and macrophages were labelled, as were gemistocytic astrocytes in tumour tissue. Lymphocytes were observed around vessels or scattered in tumour tissue, but none of these were labelled. Patient 8, who harboured an anaplastic astrocytoma, and Patient 9, with a mixed glioma—both infused intravenously with 10 mCi of ^{3}H-TdR—demonstrated very few labelled cells throughout the tissue examined. It was surprising to note that a few labelled cells still remained in the tumour of Patient 9 (fig. 7) seven years after the pulse of ^{3}H-TdR.

DISCUSSION

Some theoretical background is requisite to the interpretation of our observations.

The population of neoplastic cells in a glioma, as in any tumour, are divided into a proliferating and a non-proliferating pool. Cells in the proliferating pool are responsible for adding new cells to the tumour by repeating the mitotic cycle. In ordinary light microscopic preparations, only the mitotic phase of the cell cycle can be identified. Cells in the S (DNA-synthetic) phase incorporate ^{3}H-TdR into their nuclei and can thus be identified by autoradiography. All cells in S phase during the fifteen- to thirty-minute availability of a pulse of ^{3}H-TdR are labelled provided that the perfusion is adequate to expose the cells to the labelled nucleotide (Chang and Looney, 1965).

Once ^{3}H-TdR (with a half-life of twelve years) is incorporated into the DNA of a cell, it remains there until the cell either dies and releases its nuclear material or divides and shares the labelled DNA with its two daughter cells. Since each daughter cell receives one-half of the labelled DNA, several successive mitotic divisions will dilute the tritiated DNA to such a degree that the nuclei of these descendant cells will escape detection by autoradiography (Cronkite, Fliedner, Killman and Rubini, 1962; Steel, 1963). After injection of either 5 mCi of ^{3}H-TdR intra-arterially or 10 mCi intravenously, followed by exposure to photographic emulsion for four to eleven months, a labelled nucleus will contain between 50 and 100 silver grains (Hoshino, Barker and Wilson, 1975; Hoshino, Wilson and Ellis, 1975). Thus, five successive cell divisions will leave the nucleus of each descendant of maximally-labelled cells with fewer than four grains. These will be overlooked and the cells counted as unlabelled. The duration of the mitotic cycle (the cell cycle time) in human malignant gliomas has been estimated at two or three days (Hoshino, Wilson, Rosenblum and Barker, 1975; Hoshino and Wilson, 1979). After five cell cycles (approximately two weeks), all descendants of the cells labelled initially will be read as unlabelled. The detection of labelled cells two weeks after

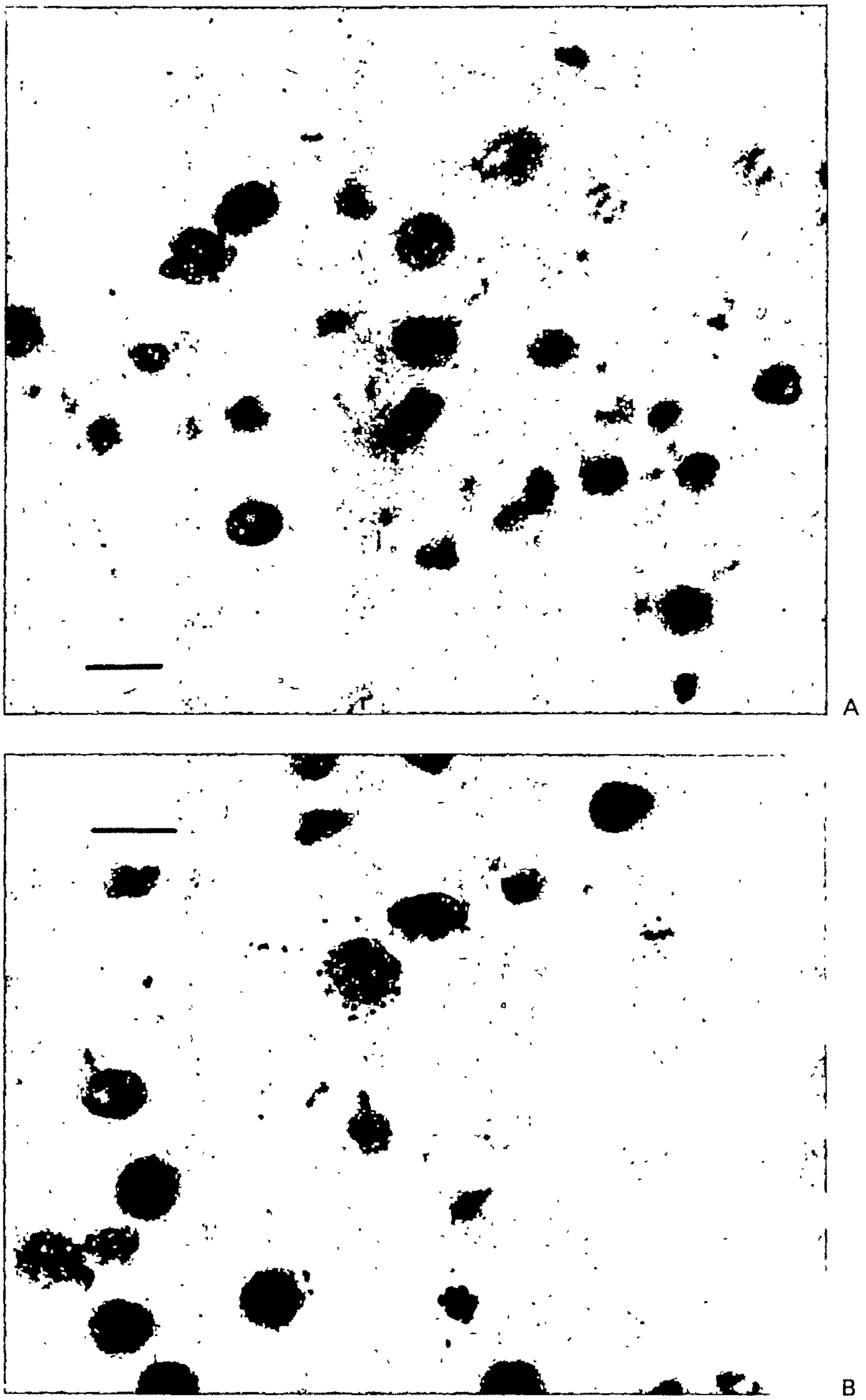

FIG. 7. A and B. Labelled cells remaining in tumour (*Patient 9*) seven years after pulse of ^{2}H-TdR. Hæmatoxylin. Bar = 20 μm.

labelling would indicate a delay in the rate of cell division. Cells found to be labelled shortly after administration of ^{3}H-TdR are generally assumed capable of proliferation, and the frequency of such labelled cells will therefore reflect the proliferative activity of the tissue (Hoshino *et al.*, 1972). Conversely, the existence of labelled cells in autopsy material obtained long after administration of ^{3}H-TdR implies retardation of proliferative activity in the labelled cells (Hoshino, Wilson and Ellis, 1975).

If, however, there is significant incorporation of labelled products from cells that die and break down, then the decrease in grain counts of dividing cells will be slower than predicted on the basis of cell cycle time. Such local salvage has been observed in rapidly growing tumours (Steel, 1966). An effect such as this may retard the decline in grain count; but if these particular cells continue to divide at the same rate, it is unlikely to result in significant numbers of labelled cells many months after the initial injection. Therefore, the presence in the same tissue of cells with many grains alongside cells with few grains can be explained as indicating that some of the cells either have a very long cell cycle time or else have ceased dividing.

As has been reported previously (Hoshino, Wilson and Ellis, 1975), no gemistocytic astrocytes were found to be labelled in any of the 9 biopsy specimens even though 8 of them contained numerous gemistocytes. However, labelled gemistocytes were present in autopsy materials as early as three weeks and as late as five months after the administration of ^{3}H-TdR. From these findings, it appears that gemistocytic astrocytes are either unable to synthesize DNA—in which case they are in the non-proliferating pool—or unable to incorporate ^{3}H-TdR. In either case, those found labelled at the time of autopsy must have existed in another morphological state when they incorporated the thymidine.

Giant cells with abundant cytoplasm, whether mononuclear or multinucleated, were sparsely labelled. These cells multiply slowly, if at all; and their origin is closely related to regressive changes within the tumour (Hoshino, Wilson and Ellis, 1975). Multinucleated giant cells with a crescentic array of nuclei appeared heavily labelled in the autopsy specimen of Patient 4, who died two months after the administration of ^{3}H-TdR. The original biopsy specimen from this patient did not contain these giant cells. In most of the multinucleated giant cells, all nuclei were labelled equally, suggesting that such cells result from a cell's repeated failure to complete cytoplasmic division, rather than from fusion of several cells. We cannot estimate the time course for induction of such cells. The presence of numerous grains above each nucleus two months after the infusion of ^{3}H-TdR (fig. 2) suggests that such cells were formed shortly after the pulse and were capable of enduring for as long as two months without successfully dividing. The chemotherapeutic agents (CCNU, procarbazine, and vincristine) administered to the patient during the two-month post-operative period could be responsible for producing this type of multinucleated giant cell. Polymorphonuclear leucocytes and macrophages in the tumour biopsy were not labelled and probably represent migrating cells, which do not divide in the tumour. At autopsy, however, these cells were labelled; these were most likely cells that were produced in the reticulo-endothelial system at the time of ^{3}H-TdR exposure and then moved to the tumour. Lymphocytes can proliferate in a tumour (as demonstrated in fig. 1), but the lack of labelled lymphocytes in the autopsy specimens implies that either they die very quickly or they continue to divide actively and thus dilute the tagged DNA.

Several subependymal astrocytes (Patients 5, 6 and 7) were found labelled (figs. 4 and 5). These may have been either normal or neoplastic cells, since tumour infiltrates were found adjacent to the ependyma. Most were heavily labelled, indicating retarded proliferative activity. They may have been astrocytes regenerating at a very slow rate, for such regeneration in the subependymal layer has been reported in animals (Hommes and Leblond, 1967; Lewis, 1968; Korr, Schultze and Mauer, 1975).

The most significant finding of this study was the variability among the 9 gliomas in the extent to which labelled cells had disappeared. In 2 cases of glioblastoma multiforme (Patients 1 and 2), the labelling had almost completely disappeared within two to four months. Three other glioblastomas (Patients 3, 4 and 5) and 2 of the anaplastic astrocytomas (Patients 6 and 7) retained some labelled cells in both the differentiated and the anaplastic areas as long as five months after the pulse of ^{3}H-TdR. Cellularity did not affect labelling. The morphology, numbers and viability of tumour cells appeared to have no bearing on the ability of these tumours to limit proliferation. For example, the growing edge of a tumour, which affords a rich environment not compromised by overcrowding, is assumed to be actively proliferating; yet the presence of many heavily labelled cells in such areas indicates that even in a favourable environment, some cells do stop dividing. Perhaps these non-dividing cells have differentiated into normal glia or surpassed some predetermined limit of cell divisions. Truly malignant cells (those with an unlimited capacity to proliferate) do not stop dividing unless there is overcrowding or a vascular crisis (as even cells *in vitro* stop proliferating when they are in plateau phase or when the medium is depleted).

Since Patients 3, 4 and 5 not only exhibited less dilution effect, but also survived for more than a year, it may be that their tumours were different from the glioblastomas of Patients 1 and 2, probably meeting Scherer's criteria for a 'secondary glioblastoma' (Schurer, 1940). These tumours could be regarded as an extreme variety of anaplastic astrocytoma, originating as astrocytoma and then undergoing malignant transformation to the histological characteristics of glioblastoma multiforme. The major difference separating them from primary glioblastoma multiforme would be their inclusion of cells that have the potential to differentiate and/or limit their own proliferation. In these secondary tumours, there should also be less frequent movement of cells between proliferating and non-proliferating pools than in primary glioblastoma multiforme. One daughter cell out of two may stop dividing (either immediately or after a few divisions), leaving the other to serve as the clonogenic cell. This would limit the number of available clonogenic cells by comparison with classic glioblastoma multiforme.

Unfortunately, there are no unequivocal histopathological patterns that definitely distinguish two separate classes of glioblastomas. The 9 cases presented here are too few to substantiate this theory. It does, however, afford a working hypothesis with which to approach to the biological behaviour of tumour groups whose proliferative activities are morphologically similar but whose responses to a particular treatment modality may vary enormously (Levin, Wilson, Davis, Wara, Pischer and Irwin, 1979).

The presence of a few labelled cells in the well differentiated mixed glioma of Patient 9 some seven years after intravenous administration of ^{3}H-TdR establishes that differentiating tumour cells can survive for as long as seven years with only a few divisions. Since most tumours of this group lack cellularity and apparently do not suffer from any nutritional deficiency, we can assume either that they have extremely long cell cycles or that almost all progeny enter non-proliferating pools from which there is very little movement back to the proliferating pool. While these inferences too are just a working hypothesis, they could be useful in designing chemotherapeutic trials. If the well differentiated gliomas have very long cell cycle times, the use of cell cycle nonspecific drugs is indicated for treatment of these tumours, thereby avoiding the toxic effect of long-term use of cell phase-specific drugs. On the other hand, if only a limited number of clonogenic cells are proliferating at a reasonable cell cycle time and there is no traffic between the proliferating and non-proliferating pools then intensive use of cell cycle specific drugs should achieve better results.

It is unfortunate that, for lack of suitable models, we cannot actually prove these hypotheses at present. Further efforts should, however, be directed to elucidation of the biological behaviour of gliomas.

SUMMARY

When ^{3}H-thymidine was administered either intravenously or intra-arterially to 9 patients with gliomas (5 glioblastoma multiforme, 3 anaplastic astrocytoma, and one mixed glioma) shortly before operation, and tissue obtained from the biopsy and, subsequently, at autopsy was examined by autoradiography, it was found that 2 of the glioblastomas diluted out the labelling in the two- to four-month interval between labelling and autopsy, whereas 3 other glioblastomas and the 2 anaplastic astrocytomas retained labelled neoplastic cells in parts of the tumours at autopsy after intervals of from three weeks to five months following labelling. Most patients whose tumours demonstrated foci of labelled cells at autopsy survived longer (1.5 to 7 years). Certain neoplastic cells in anaplastic astrocytomas and some glioblastomas appear either to limit cell division or to differentiate even in an environment favourable to cell proliferation.

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STARTLE DISEASE OR HYPEREKPLEXIA

FURTHER DELINEATION OF THE SYNDROME[1]

by FREDERICK ANDERMANN, DANIEL L. KEENE, EVA ANDERMANN *and* LUIS FELIPE QUESNEY

(*From the Department of Neurology and Neurosurgery, McGill University and the Montreal Neurological Hospital and Institute, University Street, Montreal, Quebec, Canada H3A 2B4*)

STARTLE is a basic alerting reaction common to all mammals. It is a rapid reflex not amenable to voluntary control. It was studied extensively by Strauss (1929), and is the subject of a monograph by Landis and Hunt (1939). In the human adult, except for minor interpersonal variations, a stereotyped motor pattern is seen consisting of facial grimacing, flexion of the head, elevation of the shoulders and flexion of the elbows, trunk and knees. With repeated stimulation, the intensity of the surprise reaction decreases, but it never completely disappears. Tension, fatigue and heightened expectation of the stimulus enhance it. The intensity is greater in infancy where it appears at the same time as the Moro reflex (an extensor response to sudden stimuli), but it becomes more noticeable in time as the Moro reflex disappears.

This reflex, so basic to man, can be present in a pathologically exaggerated form which is always embarrassing, sometimes interferes with normal activities, and occasionally may be dangerous. Startle disease or hyperekplexia has been the subject of a previous report by Suhren, Bruyn, and Tuynman (1966), and of a communication by Gastaut and Villeneuve (1967). The purpose of this paper is to further delineate the clinical, electrographic and genetic aspects of this disorder and to present another family with several affected members, as well as an unrelated sporadic case.

CASE REPORTS

Case 1

D.C., the proband, is a 22-year-old woman of average intelligence, the first of four children of non-consanguineous French-Canadian parents from Montreal (fig. 1).

She was born at term, after an uneventful pregnancy and labour. During the immediate neonatal period and throughout infancy, she was considered to have spastic quadriplegia. Her muscle tone, however, returned to normal in early childhood.

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She sat at 7 months and said single words at 13 months. Soon after beginning to walk at 13 months of age, her mother noted that loud noises would cause her to become stiff and fall to the ground without loss of consciousness. These episodes became so severe and frequent that she returned to crawling until she was 5 years old. She sustained two skull fractures and broke her arm during such attacks. At the age of 5 years, she started to experience episodes of clonic jerking of the limbs, lasting several minutes. These occurred mostly at night, and the lower limbs were more strikingly involved. Because these attacks were considered to be epileptic, she was treated with small doses of primidone and diphenylhydantoin.

When she was 14 years old, her mother complained about her increasingly frequent and severe falling attacks, occurring particularly at times of emotional stress or fatigue. The nature of these falls remained quite unclear until the mother described their precipitation by startle. In an attempt to evaluate this, a metal kidney basin was dropped on to a stone floor. The unexpected stimulus caused her to stiffen and fall. Characteristically, she was unable to make any attempt to protect herself or to break her fall. She did not lose consciousness, but hit her head on a metal stretcher and then cried. The unsteadiness of her gait at the time was interpreted as due to cerebellar dysfunction, and the clinical diagnosis was that of myoclonus epilepsy with ataxia or a variant of the Ramsey-Hunt Syndrome. Diazepam was added to her medication, and this reduced the frequency and severity of her falls.

She was admitted to hospital at 22 years of age together with her 13-year-old affected sister. She had a marked startle response to unexpected tactile and acoustic stimuli. In addition, tapping her forehead resulted in excessive head retraction as part of a pronounced startle response. When her medications were withdrawn, the intensity of her startle response greatly increased, and her gait became hesitant and unsure. Holding on to objects or touching the wall appeared to improve her walking and reassure her. She was often seen clinging to her sister for support, walking along the walls with a broad-based, uncertain gait.

Several falls were induced by startle and observed. She stiffened, her chin flexed, shoulders elevated, the arms remained frozen at her side, and she fell, usually backwards but occasionally forward. Several bouts of repetitive myoclonus of the limbs lasting five to fifteen minutes were observed, usually at night; again there was no loss of consciousness at the time. These were preceded by an increased feeling of unsteadiness and fear of falling, lasting fifteen to thirty minutes.

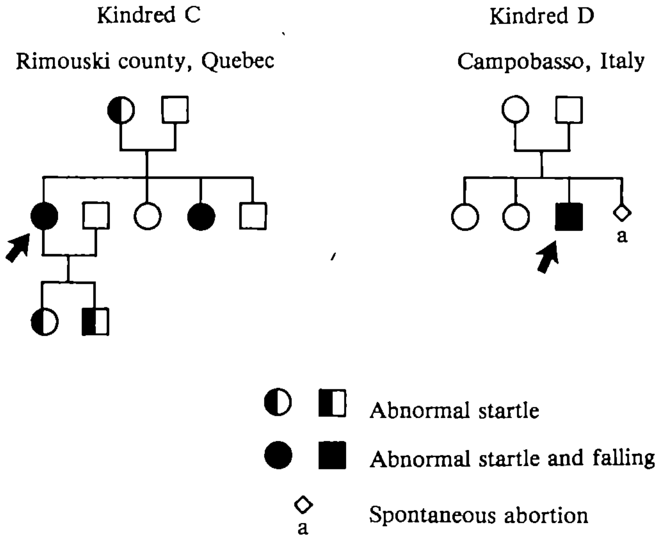

FIG. 1. Pedigrees and geographical origin of the patients.

On examination she was hyperreflexic throughout with a few beats of clonus in both ankles. Plantar responses were flexor. Rapid alternating movements of both hands were slow. No cerebellar abnormalities were found to explain her uncertain gait.

Full blood count, urine, skull films and CAT scan were normal. An EEG showed a mild, generalized, intermittent disturbance of cerebral acitivity with no epileptiform potentials. Her response to startle was studied with polygraphic recording using EEG, ECG, and submental, deltoid and quadriceps EMG. The EEG response to startle stimuli consisted of an initial spike recorded from both centro-parieto-occipital regions followed by a short lasting train of slow waves and then desynchronization of background activity lasting two to three seconds. Phasic muscle contractions were recorded from EMG leads, usually lasting up to three seconds. In addition, eye movement artefact was recorded from both frontal EEG leads (fig. 2). Five mg of diazepam administered intravenously blocked these responses almost completely, but the blinking artefact persisted (fig. 3).

An attack of generalized repetitive jerking was induced by loud noise during EEG recording; the jerks were of large amplitude, involved the lower extremities more than the upper and lasted for fifteen minutes. Extending her legs on command, attempting to elicit the knee jerks or ankle clonus greatly enhanced the movements. She remained fully conscious throughout the attack. During this episode the EEG was obscured by continuous muscle artefact.

Because of her encouraging response to diazepam, she was started on clonazepam, 2 mg by mouth twice a day. This abolished the falling attacks and the prolonged episodes of generalized jerking. The startle response was improved, but remained excessive, particularly with glabellar tapping. Her gait became much more free and secure. The hyperreflexia remained unchanged.

Case 2

M.C., the 13-year-old sister of the proband, was born at term after an uneventful pregnancy and labour. At 2 days of age she developed episodes of intermittent stiffening of the limbs, accompanied by incontinence of urine. These were precipitated by handling, and were considered to be seizures. She was treated with diphenylhydantoin. In the neonatal period, she was thought to have a spastic quadriplegia. However, on neurological examinations at age one year and over, tone was described as normal.

Developmental milestones were normal, and she was first able to walk alone at 13 months. However, she preferred to crawl, as sudden loud noises would cause her to become stiff and fall without loss of consciousness. She did this progressively less often, and finally stopped crawling at the age of 5 years. Episodes of jerking of the limbs were reported. Their duration was of the order of minutes. They occurred more frequently at night, and the legs were more severely involved than the arms.

She was investigated in hospital at the age of 13 years. She had congenital nystagmus, low in amplitude and present on all directions of gaze. Neuro-ophthalmological examination was otherwise normal, and she was the only one in the family affected by this oculomotor disorder.

Like her sister, her gait became very uncertain when medications were discontinued. She was hyperreflexic with unsustained clonus in both ankles. Plantar responses were flexor.

Her intelligence was in the low average range; on the WISC her performance IQ was 84, the verbal 76, and full scale IQ 78. Full blood count, urine, skull films and CAT scan were normal. Her EEG showed bursts of generalized 2.5–3 Hz spike-and-wave discharges lasting two to four seconds, without clinical accompaniment. They were enhanced by photic stimulation and hyperventilation.

A polygraphic study confirmed the presence of a pathological startle response which was entirely similar to that of her sister. The spike-and-wave discharge was blocked by startle (fig. 4) and the clinical startle response never induced spike-and-wave or other epileptiform discharges.

Treatment with 1 mg of clonazepam twice daily led to striking improvement in her gait, which became more secure and firm; her falling attacks ceased and her startle reactions, though still abnormal, were much diminished.

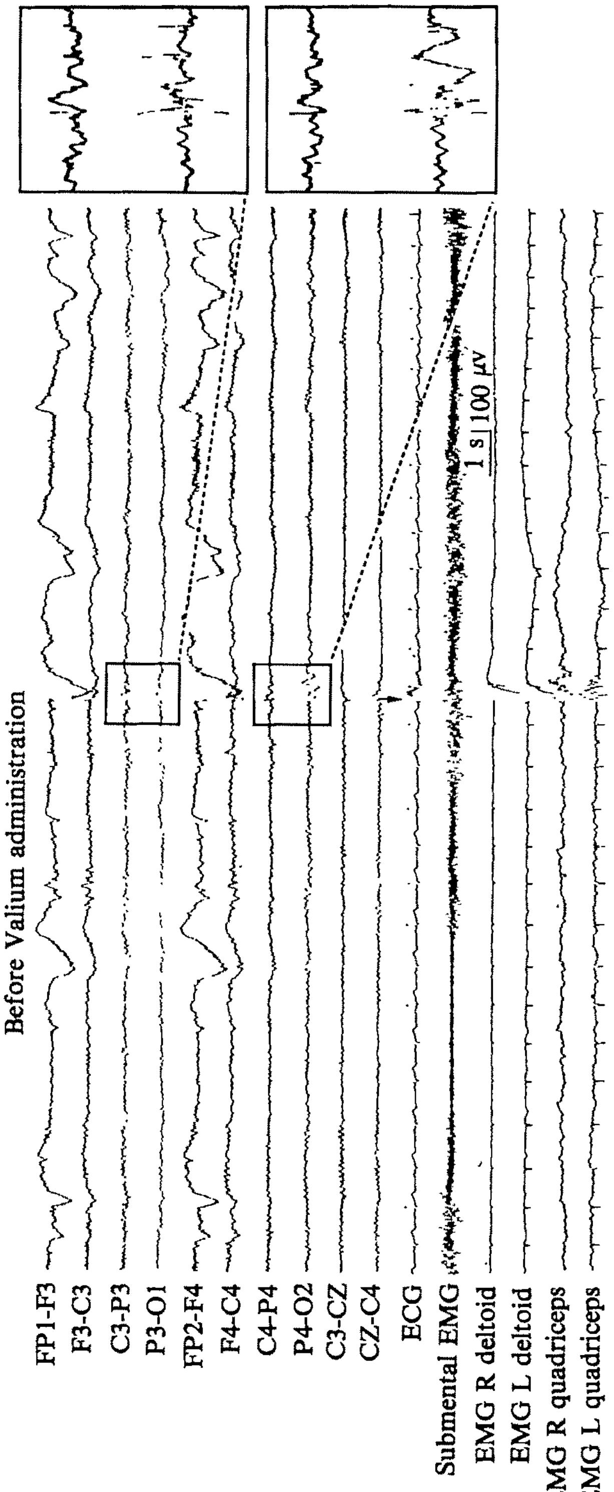

FIG. 2. Polygraphic recording of Case 1 illustrating a pathological startle response induced by noise stimulation (arrows) before intravenous Valium administration. The EEG response (*inserts*) consisted of an initial spike recorded from both centro-parieto-occipital regions followed by a short train of slow waves and transient desynchronization of EEG background activity. (In all EEG illustrations Fp, F, C, P and O correspond to fronto-polar, midfrontal, central, parietal and occipital brain regions, respectively. Uneven numbers represent left hemisphere and even numbers right. Cz = vertex.)

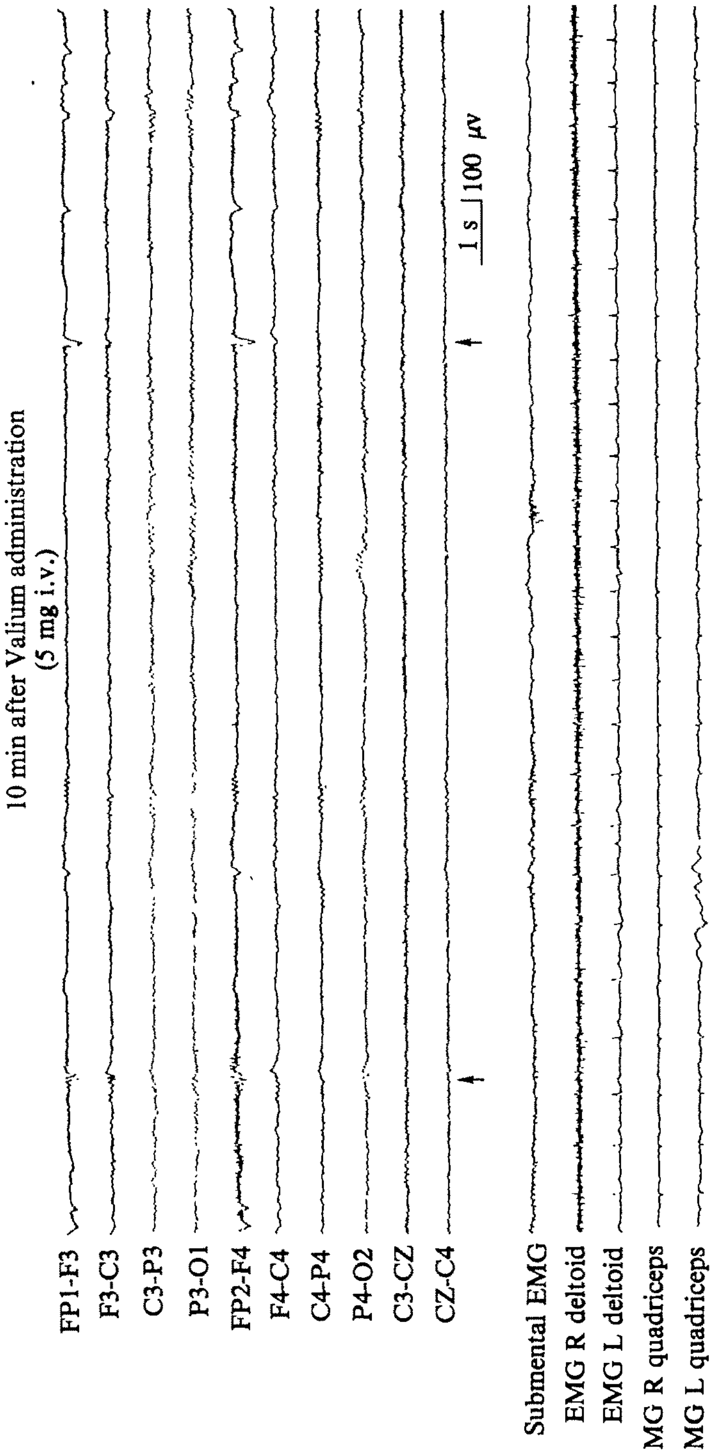

FIG. 3. Blockade of the startle response after intravenous Valium administration in Case 1.

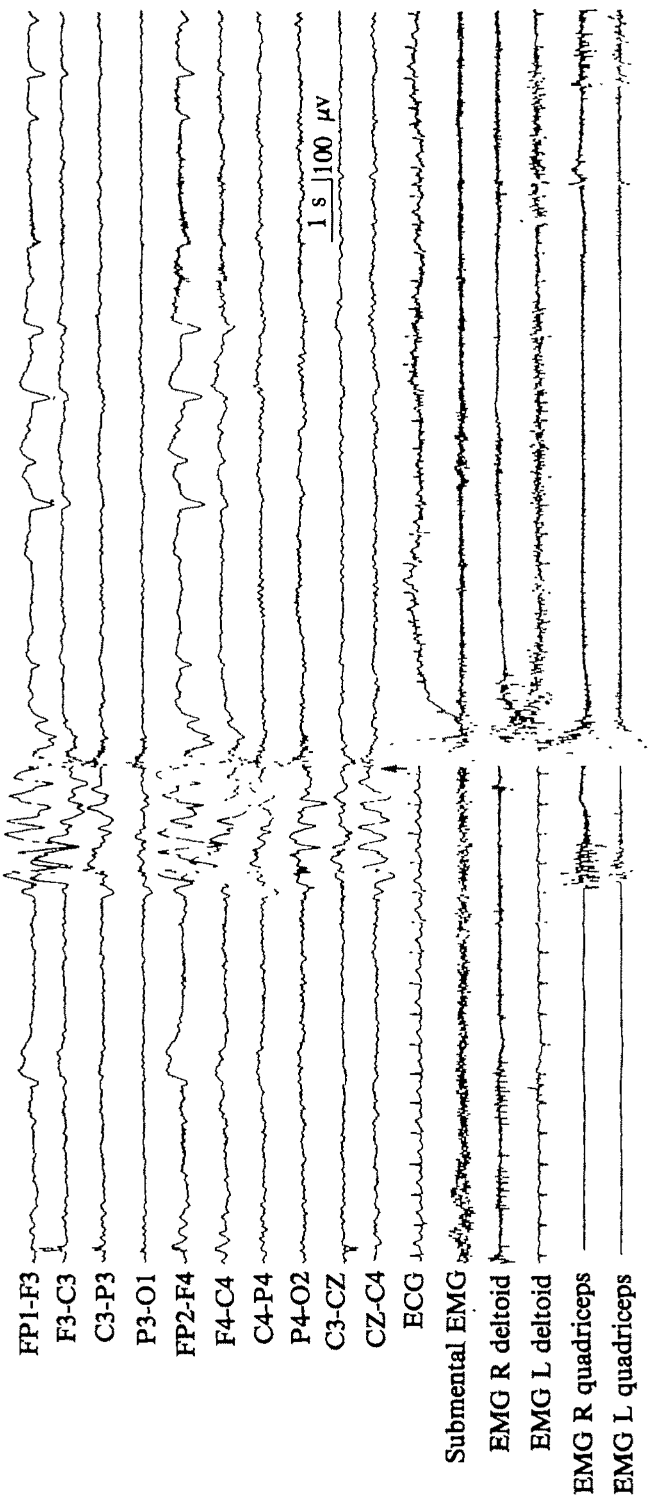

FIG. 4. *Case 2*. Startle blocks a spontaneous burst of spike-and-wave discharge.

The C family. (*See* fig. 1.) D.C., the proband, was married at the age of 18 years and was the mother of two children. Her daughter had severe single generalized jerks when startled at the age of 3 to 4 months. These only occurred during periods when she had gastroenteritis or was otherwise ill. Her son had a similar history. Both children were normal on examination at ages 3 years and 1 year 6 months, respectively. Specifically, they did not have abnormal startle, were not hypertonic, had no episodes of repetitive jerking, and their EEGs were normal.

The mother of the proband, aged 48 years, was of average intelligence and her neurological examination was normal. She did not startle excessively on examination. Her husband, however, described excessive startle during years of emotional stress which decreased to normal as her social situation improved.

We were not able to obtain a history of abnormal startle in other members of this family.

Case 3

S.D., a 12-year-old, right-handed, Italian boy, is the third child of a non-consanguineous couple from the province of Campobasso (fig. 1). He was born at term after an uneventful pregnancy and labour, weighing 4260 g, and had an Apgar of 10 at five minutes. At 2 days of age, he began to have intermittent episodes of stiffening, particularly when handled. These episodes were considered by one of us to be epileptic seizures, and he was treated with phenobarbital; because they did not stop, diphenylhydantoin was later added.

Early on, a diagnosis of spastic quadriparesis was made because of his generalized hypertonia and this, combined with the continuing attacks, led to considerable concern about his eventual prognosis.

He crawled at 9 months, walked and began to talk at 18 months, and the hypertonia was no longer present at that time. However, soon after assuming the upright stance, it was noted that sudden noises or unexpected touch would cause him to become stiff and fall without loss of consciousness.

At 4 or 5 years of age, nocturnal episodes consisting mainly of lower limb jerking of uncertain duration began. Since his falls had almost completely ceased at the age of 10, and there was some question as to the nature of his attacks, the diphenylhydantoin and phenobarbital were stopped. Shortly thereafter, he went fishing and caught a small fish; when he pulled it out of the water, it landed on him and he promptly collapsed. Another day, a grasshopper jumped on him in the field and he had a similar episode. Since his nocturnal jerks increased at the same time, the medication was restarted.

A diagnosis of myoclonus epilepsy with cerebellar involvement was entertained mainly because of his uncertain gait, attributed to cerebellar deficit. An EEG showed a sharp wave focus at the parietal vertex.

In hospital, at the age of 12 years, he was found to be hyperreflexic, but had no abnormal reflexes. He startled excessively to a variety of stimuli, and responded with pronounced head retraction to glabellar tapping. When his medication was stopped, his gait became very uncertain and he was reluctant to leave the bed. He tended to clutch people or furniture and touched the wall for support. The startle greatly increased and at times he fell forward or backward without being able to protect himself, but did not lose consciousness. His intelligence was low average, and he had learning and behavioural problems.

Blood count, urine including urinary amino acids, skull films and CAT scan were normal. His EEG showed intermittent nonspecific slow wave activity in the theta frequency range from both centrotemporal regions, but the previously recorded vertex sharp discharges had disappeared. A polygraphic study was carried out. Startle induced a response strikingly similar to the findings in the previous two patients. The response to clonazepam was also very similar and pronounced: for the first time, he was able to walk freely on a subway platform without having to remain within reach of the wall at all times.

No similar cases are known in his family and neither his parents nor his siblings have ever had excessive responses to startle.

DISCUSSION

Startle as a consequence of sudden stimuli is a normal reflex. It occurs for a fleeting moment, suspending or replacing all other motor activity. This reaction cannot be prevented voluntarily.

In normal individuals, excessive startle occurs as a manifestation of tension, fatigue and sleep deprivation. In this situation, it represents accentuation of the normal, phylogenetically determined response. In patients with tension states and anxiety neuroses, the response is also very pronounced. There is probably a genetic predisposition to startle in the general population which possibly follows a normal distribution like that of other biological phenomena, accounting for the variability of the response. However, neither when fatigued nor under stress does the normal person exhibit startle to the degree of the patients described here. When startled, in addition to a grossly exaggerated response, these patients lose their balance and fall, often injuring themselves. They also have violent, mainly nocturnal, repetitive jerks of the extremities; transient generalized hypertonia in the first year of life; hyperreflexia; and a peculiar, insecure gait.

These patients are strikingly similar to those described by Suhren *et al.* (1966). They used the term hyperexplexia to describe the startle disease they encountered in 25 members of a Dutch family over 5 generations. Their patients had an excessive response to startle elicited by stimuli which would fail to produce a startle response in most normal individuals. The disorder occurred in two forms: a minor form, in which the response was quantitatively different (that is, the movements were more

Table 1. The Two Forms of Startle Disease or Hyperekplexia

- Major
  - Transient hypertonia in infancy
  - Excessive startle response
  - Falling attacks without unconsciousness
  - Episodic generalized shaking
  - Generalized hyperreflexia
  - Insecure hesitating gait
- Minor
  - Inconstant excessive startle response

violent than normal); and a major form, in which there were also additional clinical symptoms. In the major form, the patients experienced momentary generalized muscular stiffness with loss of voluntary postural control causing them to fall, as if frozen, with their arms at their sides, unable to carry out protective movements. As soon as they hit the ground, muscle tone and control of voluntary movements returned, and there was never evidence of loss of consciousness. This abnormal response was present from the time the affected child first attempted to walk. It was increased by emotional tension, nervousness, fatigue and the expectation of being frightened, while alcohol, phenobarbital, and chlordiazepoxide lessened its intensity to some degree.

In the major form, there was transient generalized hypertonia during infancy. As babies, when awakened or handled, they had an immediate increase in muscle tone, which disappeared during sleep. This abnormality diminished as spontaneous activity increased during the first year of life. Around the time of its disappearance, frequent violent and often repetitive jerks of the limbs were described as the child fell off to sleep. These jerks could lift the child off the bed.

As illustrated by the large family of Suhren *et al.* (1966) and by our first family, the major and minor forms of abnormal startle can occur in the same family. A parent with the minor form can have children with the major form and *vice versa*, but siblings tend to be affected to the same degree. Therefore, we agree with the conclusion of Suhren *et al.* (1966) that these two forms represent different phenotypic expressions of the same autosomal dominant gene.

The diagnosis of startle disease should not be difficult if one is aware of this syndrome. The condition is probably rare and one would suspect that it is commonly misdiagnosed as epilepsy, as it was at first in our patients. The hypertonia in early life is easily interpreted as spastic-quadriplegia, as it was in our cases, and its disappearance is quite baffling. The most puzzling symptom is the unsteady gait suggesting, as it did to us, a cerebellar disorder rather than the uncertainty and fear of falling which it represents.

Suhren *et al.* (1966) considered the disorder to be non-epileptic, and we would certainly agree with this interpretation. They felt that the abnormality in these patients was likely due to retardation in maturation of control of brain-stem centres by higher inhibitory mechanisms, particularly by the rhombo-mesencephalic reticular formation. There is, however, in some of the patients, evidence for more widespread cerebral dysfunction, not explainable by a maturational defect in a specific system. Thus, one of our patients had an active spike-and-wave discharge and another a parietal sharp wave focus, though neither had epileptic seizures or episodes other than the specific clinical phenomena just described. Indeed, the epileptic discharge was blocked by startle. Low average intelligence was also encountered in 2 of our 3 patients with the major form, suggesting diffuse cerebral dysfunction. The hypertonicity and hyperreflexia implied an abnormality of the pyramidal system.

A detailed description of 12 patients with startle disease was given by Gastaut and

Villeneuve (1967). These authors also stressed the psychogenic precipitation of startle and falling. Eleven of their patients had falling attacks and in at least one these were, according to their description, identical to the ones presented above. One patient had seizures and one possibly had pseudoseizures. The incidence of mild retardation or low intelligence was higher than expected and similar to what we have found. Nine had nocturnal jerking of the legs. The authors felt that their patients were different from the ones described by Suhren *et al.* (1966), though it seems likely that at least some of them had the same disorder, but without an obvious family history.

A positive family history may be difficult to elicit in this condition because of the phenotypic variation. In our first family, the disorder was obvious in the proband and her sister. Only the minor form was present in the proband's children, and that only when they were ill. It was impossible for years to obtain a history of abnormal startle from either of the parents of the proband. Eventually it became clear that, in the years leading up to the mother's divorce from her alcoholic husband, she startled excessively and literally jumped off her chair when the telephone rang. In our second family, however, no other family member was found to be affected by either the major or the minor form, even on intensive questioning. This may be explained by a new mutation in the proband, or by lack of penetrance of the gene in other family members.

Previous authors (Suhren *et al.*, 1966; Gastaut and Villeneuve, 1967) suggested that jerking of the legs occurred only at night and presumably represented an exaggerated form of hypnagogic myoclonus. Our first two patients had such attacks in the daytime as well, and all limbs were involved though the legs always more than the arms. The third patient had only nocturnal attacks. When the attacks occurred at night, the patients woke with a feeling described as unsteadiness or similar to their state when unexpected stimuli would be likely to provoke a fall. The jerking would start later and would last for several minutes. There were no electrographic features to suggest an epileptic ætiology. Clinically these attacks resembled spontaneous generalized clonus.

The EEG correlates of startle in our patients are similar to those reported by Gastaut and Villeneuve (1967) and Suhren *et al.* (1966). The EEG response consisted of an initial spike recorded from both centro-parieto-occipital regions, followed by a short-lasting train of slow waves and then desynchronization of background activity lasting two to three seconds. This complex discharge is the most consistent electrographic correlate of excessive startle, and it may represent an evoked response to various sensory stimuli.

Neither our patients nor the ones reported by Gastaut and Villeneuve (1967) had hernias. The significance of the hernias emphasized by Suhren *et al.* (1966) in this condition is uncertain, though it could be related to the hypertonicity of early life.

The course of the condition is variable according to Suhren *et al.* (1966). Some patients eventually improve, whereas in others the symptoms increase or arise later in life. In our patients, there has been little change over the years, although on the whole the manifestations were more severe in childhood, when the hypertonicity was striking and the falls very frequent.

There is no good evidence that patients with sporadic startle disease differ from the familial cases described by Suhren *et al.* (1966), as suggested by Gastaut and Villeneuve (1967). Our own cases, familial or sporadic, appear to have the same syndrome. Thus, these two forms would appear to represent a single genetically determined disorder.

As Gastaut and Villeneuve (1967) suggested, the correct Greek term describing this disorder should be hyperekplexia rather than hyperexplexia.

At the present time, clonazepam, a benzodiazepine and potent serotonin agonist, appears to be the drug of choice in the treatment of this condition. In small doses, it abolishes the falling attacks and greatly reduces the episodic jerking. Although it does not cause the startle response to return to normal, its effect is greater than that of diazepam and appears to be sustained. Phenobarbital, diphenylhydantoin and primidone, though they have some effect on the falling attacks, startle and repetitive jerks, are not the drugs of choice for treatment of this condition. These findings suggest that a serotoninergic mechanism may be involved.

Other Disorders of Startle

The earliest report in the medical literature of an abnormal reaction to sudden sensory input was Beard's presentation in 1878 to the American Neurological Association on 'The Jumping Frenchmen of Maine'. He noted that among the French Canadian lumbermen from the Moosehead Lake region of Maine, there was an often familial condition, in which if one of them was suddenly asked to strike another, he would do so without hesitation, even if it was his mother and he had an axe in his hand. If given a short, sudden, quick command, the affected person would respond with the appropriate action, often echoing the words of the command. Some, when addressed quickly in a language foreign to them, would echo the phrase, even to the point of quoting from the *Odyssey* or *Iliad* (Beard, 1880). In addition, an unexpected touch resulted in a jump of violent proportions. Excessive startle without falling and associated echopraxia and echolalia were the essential features of the syndrome Beard described. He felt that this condition was not a pathological nervous disease, but 'a fixed psychological state', 'a survival of habits' and 'a remarkable illustration of the involuntary life' (Beard, 1878).

More recently, Stevens (1965) reported three patients with excessive responses to unexpected sensory stimuli: a French-Canadian man, a Scottish-Irish-German woman, and her niece. The man would startle excessively and on several occasions fell as a consequence. From the description it is not clear whether the falls were of the type described by Suhren *et al.* (1966) and seen in our patients or whether any other clinical feature of startle disease was present. The female patient and her niece had excessive startle; the older lady had echolalia as well.

There has been no further published report on the Jumpers of Maine. However, Dr Jean-Marc Saint-Hilaire and his daughter Dr Marie-Hélène Saint-Hilaire have recently videotaped interviews with several Jumpers from the Beauce region of Quebec (personal communication). This is the area of origin of the lumbermen of the Moosehead Lake region of Maine, which is linked to the Beauce by a direct road. These individuals startle excessively but also have a history of suggestibility, echolalia and echopraxia and, when startled, may exclaim or swear. Thus, Beard's description of 1878 was remarkably accurate. There is still some question whether this disorder is culturally determined but, in view of the fact that it has a familial incidence, this is unlikely. The Jumpers of Maine seem to have a disorder different from startle disease in that echolalia, echopraxia, suggestibility and swearing are not part of the latter syndrome.

Excessive startle is also a feature of 'tic disease' or Tourette syndrome in 20 per cent of patients (Murray, 1978). Echopraxia and echolalia are seen as well in 20 per cent of patients with this condition (Shapiro, Shapiro, Bruun and Sweet, 1978). The tics themselves are not induced by startle, though they are similarly subject to precipitation by tension or fatigue. These findings, as well as the effect in Tourette syndrome of clonazepam (Gonce and Barbeau, 1977) suggest the possibility of a common disorder of serotoninergic mechanisms in the two conditions.

Epileptic startle was reviewed by Alajouanine and Gastaut (1955). It was usually found in patients with infantile hemiparesis or quadriparesis and diffuse cerebral dysfunction. In some, there were other associated epileptic manifestations during the attacks, which left little doubt as to their epileptic nature. In others, it was difficult to decide whether the abnormal startle was in itself an epileptic phenomenon. Though startle may clearly induce seizures or falling attacks in certain epileptic patients, its exact mechanism in activating these events remains unknown. Perhaps certain diffuse encephalopathies may affect the same neuronal systems and lead to similar clinical manifestations as are found in genetically determined startle disease. This, however, remains speculative. In most instances, there is little difficulty in the diagnosis of epilepsy where startle is part of that disorder. Giménez-Roldán and Martin (1979) reported that clonazepam was extremely effective in the treatment of startle-induced seizures. This observation further supports the concept of a common pathway in the pathophysiology of startle disorders.

Recognition of startle disease or hyperekplexia may avoid an incorrect diagnosis of epilepsy and lead to appropriate treatment and genetic counselling.

SUMMARY

Startle disease is an autosomal dominant disorder with two phenotypic expressions. In the major form, there is hypertonia in infancy, and later an insecure gait. The patients have falling attacks without unconsciousness and in these, they are often injured or suffer concussions. Episodes of shaking of the limbs lasting for several minutes and resembling generalized clonus or repetitive myoclonus occur. These are most often nocturnal and are also unaccompanied by loss of

consciousness. The patients are hyperreflexic and show an increased incidence of associated neurological and electroencephalographic abnormalities.

The minor form of startle disease is only manifested by excessive startle and this is inconstant. In infancy it is brought out by febrile illness and in adult life by emotional stress.

Gastaut and Villeneuve postulated the existence of a sporadic form of hyperekplexia different from the disorder described by Suhren *et al.* Review of their report and comparison with the cases of Suhren *et al.* and our own patients leads us to believe that the sporadic and familial forms of startle disease are the same.

The disorder is rare, probably misdiagnosed initially as spastic quadriplegia, and later as epilepsy. Clonazepam appears to be the treatment of choice and its effect is sustained.

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NOTICES OF RECENT PUBLICATIONS

Essays in Neurochemistry and Neuropharmacology. Vol. 4. Edited by M. B. H. Youdim, W. Lovenberg, D. F. Sharman and J. R. Lagnado. 1980. Pp. 282. Chichester: John Wiley. Price £19.50.

Volume 4 of this series is, like its predecessors, full of interesting information and, even more so, of unsolved problems likely to stimulate the reader's curiosity and, it is hoped, activity. Chapter 1 deals with schizophrenia. It is a very complete and well argued discussion of the possibilities of finding a biochemical lesion of this disease. It is somewhat disappointing that, in the author's view, of the many theories suggesting biochemical defects or abnormalities in schizophrenic patients, not a single one is considered irrefutably excluded by the evidence available. It means that more work should be expended on all the proposed hypotheses, rather than directing future attempts on some more recent lines, for example on peptide chemistry. The next two chapters describe the molecular processes responsible for release by exocytosis of catecholamines from noradrenergic terminals and from the adrenal medulla. A long sequence of rapid chemical changes involving among others calcium, nucleotides and a new protein synexin has to take place; 'modulation' of these processes by drugs form the basis of their action on transmitter release. There is an interesting discussion of the question about the role of modulation in physiological as contrasted with pharmacological events. Furthermore, the great gap is emphasized which exists between possible theories of the events underlying transmitter release or its modulation, and their demonstration by actual observations.

The next chapter is devoted to dopamine-β-hydroxylase, its chemistry and kinetics, and the discussion of the possible identity of this enzyme with chromogranin A, which is strongly disputed by some authors. Brain enolases form the next subject reviewed. These brain-specific enzymes form part of the basis of glycolysis; the neuron-specific one was previously known as protein 14.3.2, and is found in all neurones and APUD cells. Glia has its own enolase which is identical with the liver enzyme. The last chapter deals with the problem of changes in catecholamine receptor sensitivity. This problem has recently become of interest to the psychiatrist because of theories about the basis of psychoses and their treatment by drugs which appear to involve altered receptor sensitivity. The speed with which some sensitivity changes take place may also explain the adaptability of the brain to drastic variations in synaptic input.

Whoever reads this volume will not be lulled into complacency about the state of our knowledge of the problems under discussion. This is a very healthy state of affairs even if it is sometimes disappointing.

M. VOGT

Disability. *Proceedings of a Seminar on Rehabilitation of the Disabled in Relation to Clinical and Biomechanical Aspects, Costs and Effectiveness, held at the University of Strathclyde, Glasgow, in August 1978.* Edited by R. M. Kenedi, J. P. Paul and J. Hughes. 1979. Pp. 524. Price £25.00.

This book records the Proceedings of a seminar held at Strathclyde University in August 1978. The Proceedings are edited by three Professors representing prosthetics and orthotics, and bioengineering. Very little of this book is directly concerned with neurological rehabilitation and, indeed, no neurologists or neurosurgeons participated in the meeting—much of which was concerned with artificial limbs and the problems of joint replacement. None the less, some of the subject matter is of more general interest.

The book is divided into six sections. The first, entitled 'Rehabilitation Worldwide' contains some worthwhile papers on conceptual and organizational aspects of the subject. Particularly noteworthy is the chapter on rehabilitation medicine in the United Kingdom by the late Philip Nichols. This reviews the current untidy situation in this country and summarizes the debate which has been taking place as to whether there should be a speciality of rehabilitation medicine. He concludes that there is a general reluctance within the medical profession to establish a large speciality of rehabilitation medicine. However, there does appear to be a consensus of view that there is a need for a *small* speciality, based upon teaching centres, which would include a regional specialized service. The implications of this policy are that the practising clinicians would need to accept overall responsibility for the rehabilitation of their own patients. This will mean, if the policy is to be taken seriously, introducing rehabilitation medicine into training programmes for undergraduates and postgraduates. Additionally, clinicians will need to be given extra facilities and some expansion of certain specialities, including neurology, would be essential.

There is an interesting chapter on 'The Evaluation of the Ljubljana Electronic Peroneal Brace.' This device, introduced in about 1967, can be used to correct the foot drop of some hemiplegic patients. It involves the application of a tetanic stimulus to the lateral popliteal nerve. The stimulating current is triggered by an insole in the shoe which incorporates a heel switch. Thirty-six patients out of forty-three showed some improvement in gait pattern. However, there was not adequate control group. The device may be of use to a small number of patients.

Another section in this book deals with methodology in relation to some forms of disability. Two brief papers are of some neurological interest. One describes a method for quantifying irregularities of gait. The other gives details of a computerized Romberg test. Neither paper makes any real attempt to review past work or to put the data presented into perspective. Lastly, there is another general section dealing with the achievements, failures, costs and benefits of rehabilitation services—particularly in reference to the elderly.

All in all, whilst there are some articles of interest, this is not a book which can be recommended to neurologists.

R. LANGTON-HEWER

Relief of Pain in Clinical Practice. By S. Lipton. 1979. Pp. 373. Oxford: Blackwell Scientific Publications. Price £18.00.

Chronic Pain: Further Observations from City of Hope National Medical Center. Edited by B. L. Crue, Jr. 1979. Pp. 581. New York and London: SP Medical and Scientific Books. Price £31.50.

This is a very difficult time to write about pain. Paradoxes abound: for instance, whilst important advances have been made in relevant neurochemistry and neurophysiology, the clinician in the pain clinic will be less appreciative of these advances, and the patient with intractable post-herpetic neuralgia even less so. As theoretical advances occur, the gulf between the work of scientist and doctor widens, as perhaps does the gulf between doctor and patient. Within the medical profession itself, developments are often greeted with scepticism: for example, whilst Lipton devotes a tenth of his book to acupuncture and increasing numbers of doctors are taking up the technique, this form of treatment was considered 'not proven' at a recent meeting of the British Medical Association (*British Medical Journal* (1979) **2,** 1339–1342). It is also a time of disappointment: for example, hopes that the newly-found endogenous opiate-like substances would rapidly lead to powerful and non-addictive analgesics have not been realised; the inability to predict both benefit and duration of any efficacy of the various electrical pain-relieving systems is disappointing, and the indications for some of even the most commonly performed surgical procedures, for instance in the treatment of low back pain, remain unsatisfactory.

What, then, is an author aiming to achieve when he writes about pain? These two books represent the extreme possibilities. The book by Lipton—one of the foremost practitioners and promoters of the art of clinical pain relief in Britain—is a single-author, authoritative, and personal work, a summary of his accumulated experience. Crue's '*Chronic Pain*', on the other hand, consists of 42 authors' contributions, nearly all the contributors being members of the City of Hope Pain Center, California. It is the third volume to be published from the Center, and represents work and observations from the Clinic for the years 1973 to 1977.

Lipton's *Relief of Pain in Clinical Practice* comprises 14 chapters, with introductory chapters on basic treatments and an outline of relevant anatomy and physiology. These are followed by chapters on pain in the head, pain in the neck and upper limb, the intervertebral disc, treatment of cancer pain, post-herpetic neuralgia, and chapters on techniques useful in the control of pain: electric stimulation, acupuncture, and nerve blocks. It is at its best where the author is in complete command of the subject—that is, in the practical approach and management of the patient with chronic pain, as viewed by the anæsthetist (incidentally, a reflection of the minor role of the neurologist in this subject, at least in Britain). The chapter on post-herpetic neuralgia is outstanding and those on nerve blocks and the treatment of cancer pain are excellent. Where the book is less satisfactory is on the theoretical aspects: although there seems to be an irresistible tendency to include such chapters in books on pain, the information here is necessarily over-simplified and inevitably out of date, which limits its usefulness. There are also for this reviewer some striking omissions: for instance, whilst acupuncture of various types is dealt with in no less than three chapters, causalgia is hardly mentioned; and whilst the Klippel-Feil syndrome receives a paragraph, phantom pain receives three lines in passing.

The book is very well written, illustrated and produced, with useful selected references and is moderately priced. With reservations, the book can be thoroughly recommended, and much of its practical contents will be of great value to those who deal with patients with chronic pain.

Chronic Pain opens with a photograph of the 'City of Hope Chronic Benign Pain Team at weekly pain conference, discussing patients on the Pain Unit'. This epitomizes much of the book itself: that it is multi-author, collaborative, a 'house' work, and presumably carries the conviction that its experiences should be shared. The 44 chapters are divided into 7 sections: introductory, neurophysiology, neurosurgery and cancer pain, psychological aspects, the intractable pain unit, selected specific pain problems or treatment modalities, and a concluding section. Chapters range from one on the role of the dietician on the pain unit to another devoted to a case report, and from a review chapter on the non-specific thalamic system to another on 'administrative considerations of the rehabilitation aspects in the pain program'.

It is doubtful whether experience from such a clinic can easily be transmitted in book form to others. However, many readers will be intrigued to learn that the Center does not accept patients with clinically apparent suicidal risk, with medical conditions such as active rheumatoid arthritis, nor any type of active litigation. The few review articles fit uneasily and haphazardly into the book as a whole, several chapters of which have appeared years earlier. In passing, in one of the review articles, a section entitled 'Additional Recent References' that includes references going back to 1973 appears inappropriate for a book published in 1979. The individual contributions conclude with copious references, and the book is well produced. One is left wondering, however, with the ever increasing appearance of up-to-date articles dealing with recent scientific advances, and with more useful works concerned with practical aspects of patient management, whether there is any place at all for an expensive book such as this.

G. D. SCHOTT

Medical Neurology. By J. Gilroy and J. S. Meyer. 3rd Edition, 1980. Pp. 787. London: Bailliere Tindall. Price £21.00.

Although this textbook has now reached a third edition it was previously unknown to me so that I read it with fresh interest. The qualities one seeks in such a work have been discussed in previous reviews in this journal. Doctors Gilroy and Meyer provide a large comprehensive book with the bonus of a substantial and useful section on pædiatric neurology. They are at their best in the chapters which more clearly flow from their own experience, for example, those on epilepsy and cerebrovascular disease. References are plentiful and up-to-date, though once again it is strange to find a section on spinal injuries which contains no reference to the work of Guttmann.

There are certain points at which insufficient account has been taken of recently acquired knowledge, for example that relating to syringomyelia, reticulum cell sarcoma of the brain, secretory pituitary tumours, and those uncommon affections of myelin, Marchiafava-Bignami's disease and central pontine myelinolysis. The account of tetanus appears too biased in favour of acute forms of intoxication. On treatment, irradiation is still advocated for some patients with syringomyelia, and enemata are advised for the treatment of constipation in patients with multiple sclerosis; are these still employed in North America in this context? On classification, the chapter on degenerative diseases of the nervous system is a miscellany, in which hydrocephalus succeeds the Kugelberg-Welander Syndrome, followed by syringomyelia and cervical myelopathy associated with rheumatoid arthritis.

In general, the authors have succeeded in their aim of maintaining a practical and equitable balance. The literary style is good, the book is well produced, and the price is very reasonable. *Medical Neurology* is commended as a wide-ranging, thoughtful contribution.

R. A. HENSON

Constantin von Economo. The Man and the Scientist. By L. van Bogaert and J. Theodorides. 1979. Pp. 138. Verlag der Osterreichischen Akademie der Wissenschaften. Price DM 34.00.

Constantin von Economo is of course well known to neurologists both for his description of encephalitis lethargica and for his contributions to the study of the cytoarchitectonics of the brain. Less well known is the range of his other achievements. He published on the central pathways of chewing and swallowing, on the mechanism of involuntary movements and on the nature of sleep. He was a pioneer aviator and was the first Austrian to gain an international pilot's licence. He interested the Emperor Franz-Joseph and his military advisers in the potential value of aviation and with three other pilots organized manœuvres of the first voluntary military air corps. He read widely in history and literature, both ancient and modern, and developed a particular interest in anthropology and palæontology as a complement to his later anatomical investigations. In his later years he had a special interest in the relationship between cerebral structure and genius.

The present book is to be welcomed as providing an account of von Economo's varied interests and his contributions. It is particularly valuable to have translations of a number of his early papers on encephalitis lethargica and of his address on the problems of brain research delivered at the opening of the division of Brain Research of the Psychiatric Clinic in Vienna in 1931. The authors both have personal connections with von Economo and his family and their reminiscences are therefore of particular interest. It is warming to learn of von Economo's unfailing friendliness, tact and kindness and it is understandable that the authors want to pay tribute to these splendid qualities. It must be admitted, however, that the exclusive concentration on these attractive aspects of his personality makes him seem a little unreal.

Von Economo was involved in a number of controversies. That surrounding encephalitis lethargica is dealt with at length. The reader wishing to follow up the issues raised will not, however, get as much help from the book as he might expect, since the bibliography is incomplete (a number of the works referred to in the text, including the biographical memoirs of von Economo's widow, are not listed) and the references to von Economo's own work do not follow a systematic chronological or alphabetical order. Typographical errors are frequent and it is confusing on page 28 to find a heading 'Key to accompanying figure' which relates to a paper on Post-hemiplegic Chorea discussed several pages earlier, only to find that the figure itself is nine pages from the end of the book.

But one must not be churlish. We are in Professor van Bogaert's and Dr Theodorides' debt for having recorded their knowledge and understanding of von Economo. The photographs are fascinating. Irritating though some of the matters of detail are, I enjoyed reading the book and recommend it warmly to others who are interested, not only in the history of neurology, but in the pattern of intellectual life in Vienna in the first half of the century.

W. I. MCDONALD

Textbook of Child Neurology. By J. H. Menkes. 2nd Edition. 1980. Pp. 695. London: Henry Kimpton. Price £22.00.

The second edition of Dr Menkes book is welcome. By omitting the customary section on the neurological examination he has left himself additional space for the main business of the day. This is a true textbook of child neurology, for Dr Menkes and his colleagues avoid consideration of complaints which do not affect children.

There are many references, a useful feature, although Weston Hurst's initial description of acute hæmorrhagic leucoencephalitis was published in 1941, not 1947 as printed here.

Well balanced and written in an economical but very readable style, this second edition is highly recommended to personal and departmental libraries.

R. A. HENSON

FORTHCOMING EVENTS

The Third World Congress on Pain will take place in Edinburgh, Scotland, September 4–11, 1981.

For information, apply to:

Third World Congress on Pain,
University of Edinburgh,
Centre for Industrial Consultancy and Liaison,
16 George Square,
Edinburgh EH8 9LD, UK.

The Fifth International Congress on Neuromuscular Diseases will be held in Marseilles, France, from Sunday, September 12 to Friday, September 17, 1982.

For information, apply to:

Secretariat,
5th International Congress on Neuromuscular Diseases,
c/o Pr. Georges Serratrice,
CHU La Timone,
1 Chemin de l'Armée d'Afrique,
13385 Marseille 4,
France.

The Ninth International Congress on Neuropathology will be held in Vienna, Austria, from Sunday September 5 to Friday, September 10, 1982 at the Hofburg Palace Congress Centre.

For further information please contact:

Dr H. Lassmann,
c/o Wiener Medizinische Akademie,
Alser Strasse 4,
A-1090 Vienna,
Austria.

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CONTENTS

PAGE

Joint Position Sense: the Effects of Muscle Contraction. W. Z. Rymer and A. D'Almeida 1

Brain Control of Conjugate Horizontal and Vertical Eye Movements: a Survey of the Structural and Functional Correlates. Morris B. Bender 23

Supranuclear Palsy of Eyelid Closure. R. W. Ross Russell 71

Vision in the Temporal Crescent in Occipital Infarction. Sarah Benton, Ivor Levy and Michael Swash 83

Word-form Dyslexia. Elizabeth K. Warrington and Tim Shallice 99

Disordered Inhibition in Internuclear Ophthalmoplegia: Analysis of Eye Movement Recordings with Computer Simulations. Steven E. Feldon, William F. Hoyt and Lawrence Stark 113

Variability of Visual Threshold in Multiple Sclerosis: Effect of Background Luminance on Frequency of Seeing. V. H. Patterson, D. H. Foster and J. R. Heron 139

Chronic Migrainous Neuralgia: a Variant of Cluster Headache. J. M. S. Pearce .. 149

Neuropsychological Functions in the Follow-up of Transient Global Amnesia. A. Mazzucchi, G. Moretti, P. Caffara and M. Parma 161

Neurochemical Alterations in Huntington's Chorea: a Study of Post-mortem Brain Tissue. E. G. S. Spokes 179

The Basic Uniformity in Structure of the Neocortex. A. J. Rockel, R. W. Hiorns and T. P. S. Powell 221

An Electron Microscopic Study of the Types and Proportions of Neurons in the Cortex of the Motor and Visual Areas of the Cat and Rat. D. A. Winfield, K. C. Gatter and T. P. S. Powell 245

The Clinical Features of Hereditary Motor and Sensory Neuropathy Types I and II. A. E. Harding and P. K. Thomas 259

Course and Prognosis of Multiple Sclerosis Assessed by the Computerized Data Processing of 349 Patients. C. Confavreux, G. Aimard and M. Devic 281

A Physiological Mechanism of Bradykinesia. Mark Hallett and Shahram Khoshbin 301

PAGE

A Distinct Form of Adult Polyglucosan Body Disease with Massive Involvement of Central and Peripheral Neuronal Processes and Astrocytes: a Report of Four Cases and a Review of the Occurrence of Polyglucosan Bodies in Other Conditions such as Lafora's Disease and Normal Ageing. Yvon Robitaille, Stirling Carpenter, George Karpati and Salvatore DiMauro 315

The Anatomical Basis of Conduction Aphasia. Hanna Damasio and Antonio R. Damasio 337

Effects of Ageing on Local Rates of Cerebral Glucose Utilization in the Rat. C. B. Smith, C. Goochee, S. I. Rapoport and L. Sokoloff 351

Music and Language: Musical Alexia and Agraphia. John C. M. Brust 367

Anticipatory Postural Reflexes in Parkinson's Disease and Other Akinetic-rigid Syndromes and in Cerebellar Ataxia. M. M. Traub, J. C. Rothwell and C. D. Marsden 393

The Incidence and Nature of Visual Pathway Involvement in Friedreich's Ataxia. W. M. Carroll, A. Kriss, M. Baraitser, G. Barrett and A. M. Halliday .. 413

Selective Vulnerability of Neural Cells to Viral Infections. Richard T. Johnson .. 447

Familial Oculoleptomeningeal Amyloidosis. Hershel Goren, Marta C. Steinberg and Gholam H. Farboody 473

Dystrophia Myotonica and Myotonia Congenita Concurring in one Family: a Clinical and Genetic Study. C. J. Höweler, H. F. M. Busch, L. F. Bernini, E. van Loghem, P. Meera Khan and L. E. Nijenhuis 497

Nature of the Reversible White Matter Lesion in Multiple Sclerosis: Effects of Acute Inflammation on Myelinated Tissue studied in the Rabbit Eye. M. Dalakas, R. G. Wright and J. W. Prineas 515

The Duality of the Cingulate Gyrus in Monkey: Neuroanatomical Study and Functional Hypothesis. Christine Baleydier and François Mauguiere 525

Ammonia: Assessment of its Action on Postsynaptic Inhibition as a Cause of Convulsions. J. F. Iles and J. J. B. Jack 555

Clinical, Pathological, HLA Antigen and Immunological Evidence for Disease Heterogeneity in Myasthenia Gravis. D. A. S. Compston, A. Vincent, J. Newsom-Davis and J. R. Batchelor 579

Gliomatous Transformation and Demyelinating Diseases. Milne Anderson, Brodie Hughes, Michael Jefferson, W. Thomas Smith and J. A. H. Waterhouse .. 603

A New Method for the Microdissection of the Human Hypothalamus, with Mapping of Cholinergic, GABA and Catecholamine Systems in Twelve Nuclei and Areas. Hélène Langevin and Leslie L. Iversen 623

The Neurology of Visual Acuity. L. Frisén 639

Clinical and Morphological Features of Gold Neuropathy. S. M. Katrak, M. Pollock, C. P. O'Brien, H. Nukada, S. Allpress, C. Calder, D. G. Palmer, D. M. Grennan, P. L. McCormack and M. R. Laurent 671

PAGE

Hereditary Leucodystrophy in the Mouse: the New Mutant Twitcher. L. W. Duchen, Eva M. Eicher, Jean M. Jacobs, F. Scaravilli and Fernanda Teixeira 695

The Substantia Gelatinosa of the Spinal Cord: a Critical Review. F. Cervero and A. Iggo 717

Comparison of the Effects of Transcortical and Transcallosal Removal of Intraventricular Tumours. Gina Geffen, Anthony Walsh, Donald Simpson and Malcolm Jeeves 773

Paralytic Rabies: a Clinico-pathological Study. J. S. Chopra, A. K. Benerjee, J. M. K. Murthy and S. R. Pal 789

The Effect of Spinal Cord Stimulation on Function in Patients with Multiple Sclerosis. D. J. Read, W. B. Matthews and R. H. Higson 803

Paræsthesiæ from Ectopic Impulse Generation in Human Sensory Nerves. José L. Ochoa and H. Erik Torebjörk 835

The Clinical Course of Subdural Hæmatoma. A. R. Wintzen 855

A Grab Reflex in the Human Hand. M. M. Traub, J. C. Rothwell and C. D. Marsden 869

Transmission and Scanning Electron Microscopy of Spongiform Change in Creutzfeldt-Jakob Disease. S. M. Chou, W. N. Payne, C. J. Gibbs, Jr. and D. C. Gajdusek 885

Human Visual Responses in the Absence of the Geniculo-calcarine Projection. J. L. Barbur, K. H. Ruddock and Vicki A. Waterfield 905

The Pathogenesis of Ischæmic Neuronal Damage Along the Cerebral Arterial Boundary Zones in *Papio Anubis*. J. B. Brierley, Pamela F. Prior, Jane Calverley, S. J. Jackson and A. W. Brown 929

An Autoradiographic Study of Human Gliomas: Growth Kinetics of Anaplastic Astrocytoma and Glioblastoma Multiforme. T. Hoshino, J. J. Townsend, I. Muraoka and C. B. Wilson 967

Startle Disease or Hyperekplexia: Further Delineation of the Syndrome. Frederick Andermann, Daniel L. Keene, Eva Andermann and Luis Felipe Quesney .. 985

Notices of Recent Publications 219, 435, 711, 999

INDEX

TO

BRAIN

A JOURNAL OF NEUROLOGY

FOR

VOL. CIII, 1980

AUTHORS

PAGE

Aimard, G., Confavreux, C. and Devic, M.
(*See* **Confavreux, C.** *et al.*) 281

Allpress, S., Katrak, S. M., Pollock, M., O'Brien, C. P., Nukada, H., Calder, C., Palmer, D. G., Grennan, D. M., McCormack, P. L. and Laurent, M. R.
(*See* **Katrak, S. M.** *et al.*) 671

Andermann, E., Andermann, F., Keene, D. L. and Quesney, L. F.
(*See* **Andermann, F.** *et al.*) 985

Andermann, F., Keene, D. L., Andermann, E. and Quesney, L. F.
Startle Disease or Hyperekplexia: Further Delineation of the Syndrome .. 985

Anderson, M., Hughes, B., Jefferson, M., Smith, W. T. and Waterhouse, J. A. H.
Gliomatous Transformation and Demyelinating Diseases 603

Baleydier, C. and Mauguiere, F.
The Duality of the Cingulate Gyrus in Monkey: Neuroanatomical Study and Functional Hypothesis 525

Baraitser, M., Carroll, W. M., Kriss, A., Barrett, G. and Halliday, A. M.
(*See* **Carroll, W. M.** *et al.*) 413

Barbur, J. L., Ruddock, K. H. and Waterfield, V. A.
Human Visual Responses in the Absence of the Geniculo-calcarine Projection 905

Barrett, G., Carroll, W. M., Kriss, A., Baraitser, M. and Halliday, A. M.
(*See* **Carroll, W. M.** *et al.*) 413

Batchelor, J. R., Compston, D. A. S., Vincent, A. and Newsom-Davis, J.
(*See* **Compston, D. A. S.** *et al.*) 579

PAGE

Bender, M. B.
Brain Control of Conjugate Horizontal and Vertical Eye Movements: a Survey of the Structural and Functional Correlates 23

Benerjee, A. K., Chopra, J. S., Murthy, J. M. K. and Pal, S. R.
(*See* **Chopra, J. S.** *et al.*) 789

Benton, S., Levy, I. and Swash, M.
Vision in the Temporal Crescent in Occipital Infarction 83

Bernini, L. F., Höweler, C. J., Busch, H. F. M., van Loghem, E., Khan, P. M. and Nijenhuis, L. E.
(*See* **Höweler, C. J.** *et al.*) 497

Brierley, J. B., Prior, P. F., Calverley, J., Jackson, S. J. and Brown, A. W.
The Pathogenesis of Ischæmic Neuronal Damage Along the Cerebral Arterial Boundary Zones in *Papio Anubis* 929

Brown, A. W., Brierley, J. B., Prior, P. F., Calverley, J. and Jackson, S. J.
(*See* **Brierley, J. B.** *et al.*) 929

Brust, J. C. M.
Music and Language: Musical Alexia and Agraphia 367

Busch, H. F. M., Höweler, C. J., Bernini, L. F., van Loghem, E., Khan, P. M. and Nijenhuis, L. E.
(*See* **Höweler, C. J.** *et al.*) 497

Caffara, P., Mazzucchi, A., Moretti, G. and Parma, M.
(*See* **Mazzucchi, A.** *et al.*) 161

Calder, C., Katrak, S. M., Pollock, M., O'Brien, C. P., Nukada, H., Allpress, S., Palmer, D. G., Grennan, D. M., McCormack, P. L. and Laurent, M. R.
(*See* **Katrak, S. M.** *et al.*) 671

Calverley, J., Brierley, J. B., Prior, P. F., Jackson, S. J. and Brown, A. W.
(*See* **Brierley, J. B.** *et al.*) 929

Carpenter, S., Robitaille, Y., Karpati, G. and DiMauro, S.
(*See* **Robitaille, Y.** *et al.*) 315

Carroll, W. M., Kriss, A., Baraitser, M., Barrett, G. and Halliday, A. M.
The Incidence and Nature of Visual Pathway Involvement in Friedreich's Ataxia 413

Cervero, F. and Iggo, A.
The Substantia Gelatinosa of the Spinal Cord: a Critical Review 717

Chopra, J. S., Benerjee, A. K., Murthy, J. M. K. and Pal, S. R.
Paralytic Rabies: a Clinico-pathological Study 789

Chou, S. M., Payne, W. N., Gibbs, Jr., C. J. and Gajdusek, D. C.
Transmission and Scanning Electron Microscopy of Spongiform Change in Creutzfeldt-Jacob Disease 885

PAGE

Compston, D. A. S., Vincent, A., Newsom-Davis, J. and Batchelor, J. R.
Clinical, Pathological, HLA Antigen and Immunological Evidence for Disease Heterogeneity in Myasthenia Gravis 579

Confavreux, C., Aimard, G. and Devic, M.
Course and Prognosis of Multiple Sclerosis Assessed by the Computerized Data Processing of 349 Patients 281

Dalakas, M., Wright, R. G. and Prineas, J. W.
Nature of the Reversible White Matter Lesion in Multiple Sclerosis: Effects of Acute Inflammation in Myelinated Tissue Studied in the Rabbit Eye 515

D'Almeida, A. and Rymer, W. Z.
(*See* **Rymer, W. Z. and D'Almeida, A.**) 1

Damasio, A. R. and Damasio, H.
(*See* **Damasio, H. and Damasio, A. R.**) 337

Damasio, H. and Damasio, A. R.
The Anatomical Basis of Conduction Aphasia 337

Devic, M., Confavreux, C. and Aimard, G.
(*See* **Confavreux, C.** *et al.*) 281

DiMauro, S., Robitaille, Y., Carpenter, S. and Karpati, G.
(*See* **Robitaille, Y.** *et al.*) 315

Duchen, L. W., Eicher, E. M., Jacobs, J. M., Scaravilli, F. and Teixeira, F.
Hereditary Leucodystrophy in the Mouse: the New Mutant Twitcher 695

Eicher, E. M., Duchen, L. W., Jacobs, J. M., Scaravilli, F. and Teixeira, F.
(*See* **Duchen, L. W.** *et al.*) 695

Farboody, G. H., Goren, H. and Steinberg, M. C.
(*See* **Goren, H.** *et al.*) 473

Feldon, S. E., Hoyt, W. F. and Stark, L.
Disordered Inhibition in Internuclear Ophthalmoplegia: Analysis of Eye Movement Recordings with Computer Simulations 113

Foster, D. H., Patterson, V. H. and Heron, J. R.
(*See* **Patterson, V. H.** *et al.*) 139

Frisén, L.
The Neurology of Visual Acuity 639

Gajdusek, D. C., Chou, S. M., Payne, W. N. and Gibbs, Jr., C. J.
(*See* **Chou, S. M.** *et al.*) 885

Gatter, K. C., Winfield, D. A. and Powell, T. P. S.
(*See* **Winfield, D. A.** *et al.*) 245

Geffen, G., Walsh, A., Simpson, D. and Jeeves, M.
Comparison of the Effects of Transcortical and Transcallosal Removal of Intraventricular Tumours 773

PAGE

Gibbs, Jr., C. J., Chou, S. M., Payne, W. N. and Gajdusek, D. C.
(*See* **Chou, S. M.** *et al.*) 885

Goochee, C., Smith, C. B., Rapoport, S. I. and Sokoloff, L.
(*See* **Smith, C. B.** *et al.*) 351

Goren, H., Steinberg, M. C. and Farboody, G. H.
Familial Oculoleptomeningeal Amyloidosis 473

Grennan, D. M., Katrak, S. M., Pollock, M., O'Brien, C. P., Nukada, H., Allpress, S., Calder, C., Palmer, D. G., McCormack, P. L. and Laurent, M. R.
(*See* **Katrak, S. M.** *et al.*) 671

Hallett, M. and Khoshbin, S.
A Physiological Mechanism of Bradykinesia 301

Halliday, A. M., Carroll, W. M., Kriss, A., Baraitser, M. and Barrett, G.
(*See* **Carroll, W. M.** *et al.*) 413

Harding, A. E. and Thomas, P. K.
The Clinical Features of Hereditary Motor and Sensory Neuropathy Types I and II 259

Heron, J. R., Patterson, V. H. and Foster, D. H.
(*See* **Patterson, V. H.** *et al.*) 139

Higson, R. H., Read, D. J. and Matthews, W. B.
(*See* **Read, D. J.** *et al.*).. 803

Hiorns, R. W., Rockel, A. J. and Powell, T. P. S.
(*See* **Rockel, A. J.** *et al.*) 221

Hoshino, T., Townsend, J. J., Muraoka, I. and Wilson, C. B.
An Autoradiographic Study of Human Gliomas: Growth Kinetics of Anaplastic Astrocytoma and Glioblastoma Multiforme 967

Höweler, C. J., Busch, H. F. M., Bernini, L. F., van Loghem, E., Khan, P. M. and Nijenhuis, L. E.
Dystrophia Myotonica and Myotonia Congenita Concurring in One Family: a Clinical and Genetic Study 497

Hoyt, W. F., Feldon, S. E. and Stark, L.
(*See* **Feldon, S. E.** *et al.*) 113

Hughes, B., Anderson, M., Jefferson, M., Smith, W. T. and Waterhouse, J. A. H.
(*See* **Anderson, M.** *et al.*) 603

Iggo, A. and Cervero, F.
(*See* **Cervero, F. and Iggo, A.**) 717

Iles, J. F. and Jack, J. J. B.
Ammonia: Assessment of its Action on Postsynaptic Inhibition as a Cause of Convulsions 555

PAGE

Iversen, L. L. and Langevin, H.
(*See* **Langevin, H. and Iversen, L. L.**) 623

Jack, J. J. B. and Iles, J. F.
(*See* **Iles, J. F. and Jack, J. J. B.**) 555

Jackson, S. J., Brierley, J. B., Prior, P. F., Calverley, J. and Brown, A. W.
(*See* **Brierley, J. B.** *et al.*) 929

Jacobs, J. M., Duchen, L. W., Eicher, E. M., Scaravilli, F. and Teixeira, F.
(*See* **Duchen, L. W.** *et al.*) 695

Jeeves, M., Geffen, G., Walsh, A. and Simpson, D.
(*See* **Geffen, G.** *et al.*) 773

Jefferson, M., Anderson, M., Hughes, B., Smith, W. T. and Waterhouse, J. A. H.
(*See* **Anderson, M.** *et al.*) 603

Johnson, R. T.
Selective Vulnerability of Neural Cells to Viral Infections 447

Karpati, G., Robitaille, Y., Carpenter, S. and DiMauro, S.
(*See* **Robitaille, Y.** *et al.*) 315

Katrak, S. M., Pollock, M., O'Brien, C. P., Nukada, H., Allpress, S., Calder, C., Palmer, D. G., Grennan, D. M., McCormack, P. L. and Laurent, M. R.
Clinical and Morphological Features of Gold Neuropathy 671

Keene, D. L., Andermann, F., Andermann, E. and Quesney, L. F.
(*See* **Andermann, F.** *et al.*) 985

Khan, P. M., Höweler, C. J., Busch, H. F. M., Bernini, L. F., van Loghem, E. and Nijenhuis, L. E.
(*See* **Höweler, C. J.** *et al.*) 497

Khoshbin, S. and Hallett, M.
(*See* **Hallett, M. and Khoshbin, S.**) 301

Kriss, A., Carroll, W. M., Baraitser, M., Barrett, G. and Halliday, A. M.
(*See* **Carroll, W. M.** *et al.*) 413

Langevin, H. and Iversen, L. L.
A New Method for the Microdissection of the Human Hypothalamus, with Mapping of Cholinergic, GABA and Catecholamine Systems in Twelve Nuclei and Areas 623

Laurent, M. R., Katrak, S. M., Pollock, M., O'Brien, C. P., Nukada, H., Allpress, S., Calder, C., Palmer, D. G., Grennan, D. M. and McCormack, P. L.
(*See* **Katrak, S. M.** *et al.*) 671

Levy, I., Benton, S. and Swash, M.
(*See* **Benton, S.** *et al.*) 83

PAGE

Loghem, E. van, Höweler, C. J., Busch, H. F. M., Bernini, L. F., Khan, P. M. and Nijenhuis, L. E.
(*See* **Höweler, C. J.** *et al.*) 497

McCormack, P. L., Katrak, S. M., Pollock, M., O'Brien, C. P., Nukuda, H., Allpress, S., Calder, C., Palmer, D. G., Grennan, D. M. and Laurent, M. R.
(*See* **Katrak, S. M.** *et al.*) 671

Marsden, C. D., Traub, M. M. and Rothwell, J. C.
(*See* **Traub, M. M.** *et al.*) 393, 869

Matthews, W. B., Read, D. J. and Higson, R. H.
(*See* **Read, D. J.** *et al.*) 803

Mauguiere, F. and Baleydier, C.
(*See* **Baleydier, C. and Manguiere, F.**) 525

Mazzucchi, A., Moretti, G., Caffara, P. and Parma, M.
Neuropsychological Functions in the Follow-up of Transient Global Amnesia 161

Moretti, G., Mazzucchi, A., Caffara, P. and Parma, M.
(*See* **Mazzucchi, A.** *et al.*) 161

Muraoka, I., Hoshino, T., Townsend, J. J. and Wilson, C. B.
(*See* **Hoshino, T.** *et al.*) 967

Murthy, J. M. K., Chopra, J. S., Benerjee, A. K. and Pal, S. R.
(*See* **Chopra, J. S.** *et al.*) 789

Newsom-Davis, J., Compston, D. A. S., Vincent, A. and Batchelor, J. R.
(*See* **Compston, D. A. S.** *et al.*) 579

Nijenhuis, L. E., Höweler, C. J., Busch, H. F. M., Bernini, L. F., van Loghem, E. and Khan, P. M.
(*See* **Höweler, C. J.** *et al.*) 497

Nukada, H., Katrak, S. M., Pollock, M., O'Brien, C. P., Allpress, S., Calder, C., Palmer, D. G., Grennan, D. M., McCormack, P. L. and Laurent, M. R.
(*See* **Katrak, S. M.** *et al.*) 671

O'Brien, C. P., Katrak, S. M., Pollock, M., Nukada, H., Allpress, S., Calder, C., Palmer, D. G., Grennan, D. M., McCormack, P. L. and Laurent, M. R.
(*See* **Katrak, S. M.** *et al.*) 671

Ochoa, J. L. and Torebjörk, E.
Paræsthesiæ from Ectopic Impulse Generation in Human Sensory Nerves .. 835

Pal, S. R., Chopra, J. S., Benerjee, A. K. and Murthy, J. M. K.
(*See* **Chopra, J. S.** *et al.*) 789

Palmer, D. G., Katrak, S. M., Pollock, M., O'Brien, C. P., Nukada, H., Allpress, S, Calder, C., Grennan, D. M., McCormack, P. L. and Laurent, M. R.
(*See* **Katrak, S. M.** *et al.*) 671

PAGE

Parma, M., Mazzucchi, A., Moretti, G. and Caffara, P.
(*See* **Mazzucchi, A.** *et al.*) 161

Patterson, V. H., Foster, D. H. and Heron, J. R.
Variability of Visual Threshold in Multiple Sclerosis: Effect of Background Luminance on Frequency of Seeing 139

Payne, W. N., Chou, S. M., Gibbs, Jr., C. J. and Gajdusek, D. C.
(*See* **Chou, S. M.** *et al.*) 885

Pearce, J. M. S.
Chronic Migrainous Neuralgia: a Variant of Cluster Headache 149

Pollock, M., Katrak, S. M., O'Brien, C. P., Nukada, H., Allpress, S., Calder, C., Palmer, D. G., Grennan, D. M., McCormack, P. L. and Laurent, M. R.
(*See* **Katrak, S. M.** *et al.*) 671

Powell, T. P. S., Rockel, A. J. and Hiorns, R. W.
(*See* **Rockel, A. J.** *et al.*) 221

Powell, T. P. S., Winfield, D. A. and Gatter, K. C.
(*See* **Winfield, D. A.** *et al.*) 245

Prineas, J. W., Dalakas, M. and Wright, R. G.
(*See* **Dalakas, M.** *et al.*) 515

Prior, P. F., Brierley, J. B., Calverley, J., Jackson, S. J. and Brown, A. W.
(*See* **Brierley, J. B.** *et al.*) 929

Quesney, L. F., Andermann, F., Keene, D. L. and Andermann, E.
(*See* **Andermann, F.** *et al.*) 985

Rapoport, S. I., Smith, C. B., Goochee, C. and Sokoloff, L.
(*See* **Smith, C. B.** *et al.*) 351

Read, D. J., Matthews, W. B. and Higson, R. H.
The Effect of Spinal Cord Stimulation on Function in Patients with Multiple Sclerosis 803

Robitaille, Y., Carpenter, S., Karpati, G. and DiMauro, S.
A Distinct Form of Adult Polyglucosan Body Disease with Massive Involvement of Central and Peripheral Neuronal Processes and Astrocytes: a Report of Four Cases and a Review of the Occurrence of Polyglucosan Bodies in Other Conditions such as Lafora's Disease and Normal Ageing 315

Rockel, A. J., Hiorns, R. W. and Powell, T. P. S.
The Basic Uniformity in Structure of the Neocortex 221

Rothwell, J. C., Traub, M. M. and Marsden, C. D.
(*See* **Traub, M. M.** *et al.*) 393, 869

Ruddock, K. R., Barbur, J. L. and Waterfield, V. A.
(*See* **Barbur, J. L.** *et al.*) 905

PAGE

Russell, R. W. R.
Supranuclear Palsy of Eyelid Closure 71

Rymer, W. Z. and D'Almeida, A.
Joint Position Sense: the Effects of Muscle Contraction 1

Scaravilli, F., Duchen, L. W., Eicher, E. M., Jacobs, J. M. and Teixeira, F.
(*See* **Duchen, L. W.** *et al.*) 695

Shallice, T. and Warrington, E. K.
(*See* **Warrington, E. K. and Shallice, T.**) 99

Simpson, D., Geffen, G., Walsh, A. and Jeeves, M.
(*See* **Geffen, G.** *et al.*) 773

Smith, C. B., Goochee, C., Rapoport, S. I. and Sokoloff, L.
Effects of Ageing on Local Rates of Cerebral Glucose Utilization in the Rat 351

Smith, W. T., Anderson, M., Hughes, B., Jefferson, M. and Waterhouse, J. A. H.
(*See* **Anderson, M.** *et al.*) 603

Sokoloff, L., Smith, C. B., Goochee, C. and Rapoport, S. I.
(*See* **Smith, C. B.** *et al.*) 351

Spokes, E. G. S.
Neurochemical Alterations in Huntington's Chorea: a Study of Post-mortem Brain Tissue 179

Stark, L., Feldon, S. E. and Hoyt, W. F.
(*See* **Feldon, S. E.** *et al.*) 113

Steinberg, M. C., Goren, H. and Farboody, G. H.
(*See* **Goren, H.** *et al.*) 473

Swash, M., Benton, S. and Levy, I.
(*See* **Benton, S.** *et al.*) 83

Teixeira, F., Duchen, L. W., Eicher, E. M., Jacobs, J. M. and Scaravilli, F.
(*See* **Duchen, L. W.** *et al.*) 695

Thomas, P. K. and Harding, A. E.
(*See* **Harding, A. E. and Thomas, P. K.**) 259

Torebjörk, E. and Ochoa, J. L.
(*See* **Ochoa, J. L. and Torebjörk, E.**) 835

Townsend, J. J., Hoshino, T., Muraoka, I. and Wilson, C. B.
(*See* **Hoshino, T.** *et al.*) 967

Traub, M. M., Rothwell, J. C. and Marsden, C. D.
Anticipatory Postural Reflexes in Parkinson's Disease and Other Akinetic-rigid Syndromes and in Cerebellar Ataxia 393

Traub, M. M., Rothwell, J. C. and Marsden, C. D.
A Grab Reflex in the Human Hand 869

PAGE

Vincent, A., Compston, D. A. S., Newsom-Davis, J. and Batchelor, J. R.
(*See* **Compston, D. A. S.** *et al.*) 579

Walsh, A., Geffen, G., Simpson, D. and Jeeves, M.
(*See* **Geffen, G.** *et al.*) 773

Warrington, E. K. and Shallice, T.
Word-form Dyslexia 99

Waterfield, V. A., Barbur, J. L. and Ruddock, K. H.
(*See* **Barbur, J. L.** *et al.*) 905

Waterhouse, J. A. H., Anderson, M., Hughes, B., Jefferson, M. and Smith, W. T.
(*See* **Anderson, M.** *et al.*) 603

Wilson, C. B., Hoshino, T., Townsend, J. J. and Muraoka, I.
(*See* **Hoshino, T.** *et al.*) 967

Winfield, D. A., Gatter, K. C. and Powell, T. P. S.
An Electron Microscopic Study of the Types and Proportions of Neurons in the Cortex of the Motor and Visual Areas of the Cat and Rat 245

Wintzen, A. R.
The Clinical Course of Subdural Hæmatoma 853

Wright, R. G., Dalakas, M. and Prineas, J. W.
(*See* **Dalakas, M.** *et al.*) 515

SUBJECTS

PAGE

Ageing, Effects on Local Rates of Cerebral Glucose Utilization in the Rat. C. B. Smith, C. Goochee, S. I. Rapoport and L. Sokoloff 351

Agraphia and Alexia, Musical: Music and Language. J. C. M. Brust 367

Alexia and Agraphia, Musical: Music and Language. J. C. M. Brust 367

Ammonia: Assessment of its Action on Postsynaptic Inhibition as a Cause of Convulsions. J. F. Iles and J. J. B. Jack 555

Amnesia, Transient Global, Neuropsychological Functions in Follow-up of. A. Mazzucchi, G. Moretti, P. Caffara and M. Parma 161

Amyloidosis, Familial Oculoleptomeningeal. H. Goren, M. C. Steinberg and G. H. Farboody 473

Aphasia, Conduction, the Anatomical Basis of. H. Damasio and A. R. Damasio .. 337

Arterial Boundary Zones, Cerebral, Pathogenesis of Ischæmic Neuronal Damage in *Papio Anubis*. J. B. Brierley, P. F. Prior, J. Calverley, S. J. Jackson and A. W. Brown 929

Astrocytes and Neuronal Processes, Central and Peripheral, Massive Involvement of, a Distinct Form of Adult Polyglucosan Body Disease: a Report of Four Cases and a Review of the Occurrence of Polyglucosan Bodies in Other Conditions such as Lafora's Disease and Normal Ageing. Y. Robitaille, S. Carpenter, G. Karpati and S. DiMauro 315

Astrocytoma, Anaplastic, and Glioblastoma Multiforme, Autoradiographic Study of Growth Kinetics of. T. Hoshino, J. J. Townsend, I. Muraoka and C. B. Wilson 967

Baboon (*Papio Anubis*), Pathogenesis of Ischæmic Neuronal Damage along Cerebral Arterial Boundary Zones in. J. B. Brierley, P. F. Prior, J. Calverley, S. J. Jackson and A. W. Brown 929

Bradykinesia, a Physiological Mechanism of. M. Hallett and S. Khoshbin 301

Cat, Motor and Visual Areas of, Electron Microscopic Study of the Types and Proportions of Neurons in. D. A. Winfield, K. C. Gatter and T. P. S. Powell .. 245

Cerebellar Ataxia, Anticipatory Postural Reflexes in Parkinson's Disease and Other Akinetic-rigid Syndromes. M. M. Traub, J. C. Rothwell and C. D. Marsden .. 393

Chorea, Huntington's, Neurochemical Alterations in: a Study of Post-mortem Brain Tissue. E. G. S. Spokes 179

Cingulate Gyrus in Monkey, Duality of: Neuroanatomical Study and Functional Hypothesis. C. Baleydier and F. Mauguiere 525

PAGE

Cluster Headache, Chronic Migrainous Neuralgia: a Variant of. J. M. S. Pearce .. 149

Conduction Aphasia, the Anatomical Basis of. H. Damasio and A. R. Damasio .. 337

Conjugate Eye Movements, Horizontal and Vertical, Brain Control of: a Survey of the Structural and Functional Correlates. M. B. Bender .. 23

Convulsions, Assessment of Action of Ammonia on Postsynaptic Inhibition as a Cause of. J. F. Iles and J. J. B. Jack .. 555

Corpus Callosum, Comparison of the Effects of Transcortical and Transcallosal Removal of Intraventricular Tumours. G. Geffen, A. Walsh, D. Simpson and M. Jeeves .. 773

Cortex, Motor and Visual Areas of the Cat and Rat, an Electron Microscopic Study of the Types and Proportions of Neurons. D. A. Winfield, K. C. Gatter and T. P. S. Powell .. 245

Creutzfeldt-Jacob Disease, Transmission and Scanning Electron Microscopy of Spongiform Change in. S. M. Chou, W. N. Payne, C. J. Gibbs, Jr. and D. C. Gajdusek .. 885

Demyelinating Diseases, Gliomatous Transformation and. M. Anderson, B. Hughes, M. Jefferson, W. T. Smith and J. A. H. Waterhouse .. 603

Disease Heterogeneity in Myasthenia Gravis, Clinical, Pathological, HLA Antigen and Immunological Evidence for. D. A. S. Compston, A. Vincent, J. Newsom-Davis and J. R. Batchelor .. 579

Dyslexia, Word-form. E. K. Warrington and T. Shallice .. 99

Dystrophia Myotonica and Myotonia Congenita Concurring in One Family: a Clinical and Genetic Study. C. J. Höweler, H. F. M. Busch, L. F. Bernini, E. van Loghem, P. M. Khan and L. E. Nijenhuis .. 497

Eye Movement Recordings, Analysed with Computer Simulations, in Internuclear Ophthalmoplegia: Disordered Inhibition. S. E. Feldon, W. F. Hoyt and L. Stark .. 113

Eye Movements, Conjugate, Horizontal and Vertical, Brain Control of: a Survey of the Structural and Functional Correlates. M. B. Bender .. 23

Eyelid Closure, Supranuclear Palsy of. R. W. R. Russell .. 71

Friedreich's Ataxia, Visual Pathway Involvement in, the Incidence and Nature of. W. M. Carroll, A. Kriss, M. Baraitser, G. Barrett and A. M. Halliday .. 413

Geniculo-calcarine Projection, Human Visual Responses in the Absence of. J. L. Barbur, K. H. Ruddock and V. A. Waterfield .. 905

Glioblastoma Multiforme and Anaplastic Astrocytoma, Autoradiographic Study of Human Gliomas: Growth Kinetics. T. Hoshino, J. J. Townsend, I. Muraoka and C. B. Wilson .. 967

Gliomatous Transformation and Demyelinating Diseases. M. Anderson, B. Hughes, M. Jefferson, W. T. Smith and J. A. H. Waterhouse .. 603

PAGE

Global Amnesia, Transient, Neuropsychological Functions in the Follow-up of. A. Mazzucchi, G. Moretti, P. Caffara and M. Palma 161

Glucose Utilization, Cerebral, in the Rat, Effects of Ageing on Local Rates. C. B. Smith, C. Goochee, S. I. Rapoport and L. Sokoloff 351

Gold Neuropathy, Clinical and Morphological Features of. S. M. Katrak, M. Pollock, C. P. O'Brien, H. Nukada, S. Allpress, C. Calder, D. G. Palmer, D. M. Grennan, P. L. McCormack and M. R. Laurent 671

Grab Reflex in the Human Hand. M. M. Traub, J. C. Rothwell and C. D. Marsden 869

Hæmatoma, Subdural, the Clinical Course of. A. R. Wintzen 853

Hand, Human, Grab Reflex in. M. M. Traub, J. C. Rothwell and C. D. Marsden 869

Headache, Cluster, Chronic Migrainous Neuralgia: a Variant of. J. M. S. Pearce .. 149

Hereditary Motor and Sensory Neuropathy Types I and II, the Clinical Features of. A. E. Harding and P. K. Thomas 259

HLA Antigen, Clinical, Pathological and Immunological Evidence for Disease Heterogeneity in Myasthenia Gravis. D. A. S. Compston, A. Vincent, J. Newsom-Davis and J. R. Batchelor 579

Huntington's Chorea, Neurochemical Alterations in: a Study of Post-mortem Brain Tissue. E. G. S. Spokes 179

Hyperekplexia (Startle Disease): Further Delineation of the Syndrome. F. Andermann, D. L. Keene, E. Andermann and L. F. Quesney 985

Hypothalamus, Human, New Method for Microdissection of, with Mapping of Cholinergic, GABA and Catecholamine Systems in Twelve Nuclei and Areas. H. Langevin and L. L. Iversen 623

Infarction, Occipital, Vision in the Temporal Crescent in. S. Benton, I. Levy and M. Swash 83

Inhibition, Disordered, in Internuclear Ophthalmoplegia: Analysis of Eye Movement Recordings with Computer Simulations. S. E. Feldon, W. F. Hoyt and L. Stark 113

Inhibition, Postsynaptic, Action of Ammonia on, Assessment as a Cause of Convulsions. J. F. Iles and J. J. B. Jack 555

Internuclear Ophthalmoplegia, Disordered Inhibition in: Analysis of Eye Movement Recordings with Computer Simulations. S. E. Feldon, W. F. Hoyt and L. Stark 113

Intraventricular Tumours, Comparison of the Effects of Transcortical and Trancallosal Removal of. G. Geffen, A. Walsh, D. Simpson and M. Jeeves 773

Ischæmic Neuronal Damage Along the Cerebral Arterial Boundary Zones, Pathogenesis in *Papio Anubis*. J. B. Brierley, P. F. Prior, J. Calverley, S. J. Jackson and A. W. Brown 929

Joint Position Sense: the Effects of Muscle Contraction on. W. Z. Rymer and A. D'Almeida 1

PAGE

Language and Music: Musical Alexia and Agraphia. J. C. M. Brust 367

Leucodystrophy, Hereditary, in Mutant Twitcher Mouse. L. W. Duchen, E. M. Eicher, J. M. Jacobs, F. Scaravilli and F. Teixeira 695

Migrainous Neuralgia, Chronic: a Variant of Cluster Headache. J. M. S. Pearce .. 149

Monkey, Duality of the Cingulate Gyrus in: Neuroanatomical Study and Functional Hypothesis. C. Baleydier and F. Mauguiere 525

Motor and Sensory Neuropathy, Hereditary, Types I and II, the Clinical Features of: A. E. Harding and P. K. Thomas 259

Mouse, Hereditary Leucodystrophy in: the New Mutant Twitcher. L. W. Duchen, E. M. Eicher, J. M. Jacobs, F. Scaravilli and F. Teixeira 695

Multiple Sclerosis, Course and Prognosis, Assessed by the Computerized Data Processing of 349 Patients. C. Confavreux, G. Aimard and M. Devic 281

Multiple Sclerosis, Effect of Spinal Cord Stimulation on Function in Patients with. D. J. Read, W. B. Matthews and R. H. Higson 803

Multiple Sclerosis, Nature of the Reversible White Matter Lesion in: Effects of Acute Inflammation on Myelinated Tissue Studied in the Rabbit Eye. M. Dalakas, R. G. Wright and J. W. Prineas 515

Multiple Sclerosis, Variability of Visual Threshold in: Effect of Background Luminance on Frequency of Seeing. V. H. Patterson, D. H. Foster and J. R. Heron 139

Mutant Twitcher Mouse, Hereditary Leucodystrophy in. L. W. Duchen, E. M. Eicher, J. M. Jacobs, F. Scaravilli and F. Teixeira 695

Myasthenia Gravis, Clinical, Pathological, HLA Antigen and Immunological Evidence for Disease Heterogeneity in. D. A. S. Compston, A. Vincent, J. Newsom-Davis and J. R. Batchelor 579

Myotonia Congenita and Dystrophia Myotonica Concurring in One Family: a Clinical and Genetic Study. C. J. Höweler, H. F. M. Busch, L. F. Bernini, E. van Loghem, P. M. Khan and L. E. Nijenhuis 497

Neocortex, the Basic Uniformity in Structure of the. A. J. Rockel, R. W. Hiorns and T. P. S. Powell 221

Nerves, Human Sensory, Paræsthesiæ from Ectopic Impulse Generation in. J. L. Ochoa and E. Torebjörk 835

Neural Cells, Selective Vulnerability to Viral Infection. R. T. Johnson 447

Neuralgia, Chronic Migrainous: a Variant of Cluster Headache. J. M. S. Pearce .. 149

Neurochemical Alterations in Huntington's Chorea: a Study of Post-mortem Brain Tissue. E. G. S. Spokes 179

PAGE

Neuronal Processes and Astrocytes, Central and Peripheral, Massive Involvement of, a Distinct Form of Adult Polyglucosan Body Disease: a Report of Four Cases and a Review of the Occurrence of Polyglucosan Bodies in Other Conditions such as Lafora's Disease and Normal Ageing. Y. Robitaille, S. Carpenter, G. Karpati and S. DiMauro 315

Neurons, Electron Microscopic Study of the Types and Proportions, in Motor and Visual Cortical Areas of the Cat and Rat. D. A. Winfield, K. C. Gatter and T. P. S. Powell 245

Neuropathy, Gold, Clinical and Morphological Features of. S. M. Katrak, M. Pollock, C. P. O'Brien, H. Nukada, S. Allpress, C. Calder, D. G. Palmer, D. M. Grennan, P. L. McCormack and M. R. Laurent 671

Neuropathy Types I and II, Motor and Sensory, Hereditary, the Clinical Features of. A. E. Harding and P. K. Thomas 259

Neurotransmitter Systems, Mapping of, in Twelve Nuclei and Areas of Human Hypothalamus, a New Method for the Microdissection of. H. Langevin and L. L. Iversen 623

Occipital Infarction. Vision in Temporal Crescent in. S. Benton, I. Levy and M. Swash 83

Oculoleptomeningeal Amyloidosis, Familial. H. Goren, M. C. Steinberg and G. H. Farboody 473

Palsy of Eyelid Closure, Supranuclear. R. W. R. Russell 71

Paræsthesiæ from Ectopic Impusle Generation in Human Sensory Nerves. J. L. Ochoa and E. Torebjörk 835

Parkinson's Disease, Anticipatory Postural Reflexes, and other Akinetic-rigid Syndromes and in Cerebellar Ataxia. M. M. Traub, J. C. Rothwell and C. D. Marsden 393

Polyglucosan Body Disease, a Distinct Form of Adult, with Massive Involvement of Central and Peripheral Neuronal Processes and Astrocytes: a Report of Four Cases and a Review of the Occurrence of Polyglucosan Bodies in Other Conditions such as Lafora's Disease and Normal Ageing. Y. Robitaille, S. Carpenter, G. Karpati and S. DiMauro 315

Position Sense, Joint: the Effects of Muscle Contraction on. W. Z. Rymer and A. D'Almeida 1

Postural Reflexes, Anticipatory, in Parkinson's Disease and Other Akinetic-rigid Syndromes and in Cerebellar Ataxia. M. M. Traub, J. C. Rothwell and C. D. Marsden 393

Rabies, Paralytic, a Clinico-pathological Study. J. S. Chopra, A. K. Benerjee, J. M. K. Murthy and S. R. Pal 789

Rat, Motor and Visual Areas of, Electron Microscopic Study of the Types and Proportions of Neurons in. D. A. Winfield, K. C. Gatter and T. P. S. Powell 245

PAGE

Reflex, Grab, in the Human Hand. M. M. Traub, J. C. Rothwell and C. D. Marsden 869

Sensory and Motor Neuropathy, Hereditary, Types I and II, the Clinical Features of. A. E. Harding and P. K. Thomas 259

Spinal Cord, Effects of Stimulation on Function in Patients with Multiple Sclerosis. D. J. Read, W. B. Matthews and R. H. Higson 803

Spongiform Change in Creutzfeldt-Jacob Disease, Transmission and Scanning Electron Microscopy of. S. M. Chou, W. N. Payne, C. J. Gibbs, Jr. and D. C. Gajdusek 885

Startle Disease (Hyperekplexia): Further Delineation of the Syndrome. F. Andermann, D. L. Keene, E. Andermann and L. F. Quesney 985

Stimulation of Spinal Cord, Effects on Function in Patients with Multiple Sclerosis. D. J. Read, W. B. Matthews and R. H. Higson 803

Subdural Hæmatoma, the Clinical Course of. A. R. Wintzen 853

Substantia Gelatinosa of the Spinal Cord: a Critical Review. F. Cervero and A. Iggo .. 717

Temporal Crescent, Vision in, in Occipital Infarction. S. Benton, I. Levy and M. Swash 83

Transient Global Amnesia, Neuropsychological Functions in the Follow-up of. A. Mazzucchi, G. Moretti, P. Caffara and M. Palma 161

Tumours, Intraventricular, Comparison of the Effects of Transcortical and Transcallosal Removal of. G. Geffen, A. Walsh, D. Simpson and M. Jeeves .. 773

Viral Infections, Selective Vulnerability of Neural Cells to. R. T. Johnson 447

Vision in the Temporal Crescent in Occipital Infarction. S. Benton, I. Levy and M. Swash 83

Visual Acuity, the Neurology of. L. Frisén 639

Visual Pathway Involvement in Friedreich's Ataxia, the Incidence and Nature of. W. M. Carroll, A. Kriss, M. Baraitser, G. Barrett and A. M. Halliday 413

Visual Responses in Absence of the Geniculo-calcarine Projection, Human. J. L. Barbur, K. H. Ruddock and V. A. Waterfield 905

Visual Threshold, in Multiple Sclerosis, Variability of: Effect of Background Luminance on Frequency of Seeing. V. H. Patterson, D. H. Foster and J. R. Heron 139

White Matter Lesion in Multiple Sclerosis, Reversible, Nature of: Effects of Acute Inflammation on Myelinated Tissue Studied in the Rabbit Eye. M. Dalakas, R. G. Wright and J. W. Prineas 515

Word-form Dyslexia. E. K. Warrington and T. Shallice 99

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